PEDIATRIC CLINICS OF NORTH AMERICA

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Symposium on Antimicrobial Therapy

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FOREWORD

B. M. KAGAN, M.D.

The authors of the clinics in this symposium have been generous with their time and effort in presenting to the practicing physician an up-to-date review of current knowledge of antimicrobial therapy. The Editor is sincerely grateful to them.

Five years ago one of these volumes was devoted to the first such symposium on antimicrobial therapy. Since then much has been learned. Important new forms of penicillin, tetracycline, erythromycin and oleandomycin have become available. Entirely new agents such as novobiocin, colistin, paromomycin, vancomycin, ristocetin, amphotericin B and griseofulvin have increased our reserve as well as our spectrum of activity. New awareness of toxicity has developed, especially for penicillin, streptomycin and chloramphenicol. Attempts have been made to clarify the relative roles of combined and single therapy, of items such as gamma globulin, whole blood and nutritional support. Important in the total advance has been increasing knowledge of the specific causes of various disease states so that early intelligent choice can be made from among the now increased number of potent antimicrobial agents. The development of these drugs represents the most significant contribution to the reduction of morbidity and mortality in our time. The Editor hopes therefore that this volume will aid physicians in the care of their patients.

MECHANISM OF ACTION OF ANTIMICROBIAL DRUGS

W. BARRY WOOD, JR., M.D.

GARY W. ARCHER, A.B.

The practical art of antimicrobial therapy is based upon a series of empirical discoveries. Only recently has knowledge begun to accumulate on the modes of action of antibacterial drugs. The new information has been provided, for the most part, by biochemists whose interests in bacteria have stemmed from a desire to probe the metabolic mechanisms of readily manageable living cells rather than from a concern with infectious disease. Nevertheless the facts which have emerged are of importance to clinicians, for they provide the basis for a better understanding of a remarkable group of drugs.

The ultimate therapeutic effect of any antibacterial agent is the resultant of a complex combination of three-way interactions between the *drug*, the *host* and the offending *microbe*. Those involving the drug and the host belong to the realm of pharmacology, while those which concern host-parasite relations are usually considered under the heading of immunology. The third set of interactions, which relate to the drug and the parasite, constitute the subject of this review. Although the interactions of this third category, like those of the first two, are potentially bilateral, it is only in rare instances (e.g. the destruction of penicillin by bacterial penicillinase[2]) that the parasite can be shown to affect the drug. The present discussion, therefore, as implied by the title, will concern solely the action of clinically useful antimicrobial drugs upon bacteria.

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In order to elucidate the mode of action of an antibacterial drug, it is necessary to define the precise manner in which it affects the metabolism of the bacterial cell. To do this is often extremely difficult for the simple reason that the *primary* biochemical effect may be obscured by a host of *secondary* effects. The essence of the problem is to identify the primary biochemical lesion caused by the drug in the bacterial cell. Thus far the primary biochemical lesion has been defined, with reasonable certainty, in only a few cases. Each of these is discussed in the following paragraphs. Because of limitations of space, instances in which the evidence is inconclusive are merely recorded, with pertinent references, in Table 1. The list of publications in the bibliography is in no sense complete and includes few papers dealing with essentially negative findings. For fuller bibliographies the reader is referred to the recent reviews of Gale,[30] Nathenson and Strominger[51] and Brock.[10]

There are three ways in which antibacterial drugs have thus far been

TABLE 1. *Primary Biochemical Effects of Antimicrobials*

ANTIMICROBIAL AGENT	ALLEGED MODE OF ACTION
Chloramphenicol	Inhibits protein synthesis of microbial cells[10,30]
Tetracyclines	Inhibit protein synthesis of microbial cells[31]
	Interfere with electron transport enzyme system[67] (?) *
Streptomycin	Inhibits protein synthesis of bacterial cells[27]
	Increases permeability of bacterial cytoplasmic membrane[4, 5]
Penicillin	Inhibits synthesis of bacterial cell wall[30, 51]
Sulfonamides	Prevent formation of folic acid in microbial cells by competing with para-aminobenzoic acid for enzymes associated with folic acid synthesis[51]
Bacitracin	Inhibits synthesis of bacterial cell wall[1]
Polymyxin	Increases permeability of bacterial cytoplasmic membrane[53]
Para-aminosalicylic acid	Prevents formation of folic acid in microbial cells by competing with para-aminobenzoic acid for enzymes associated with folic acid synthesis[25, 37]
Isoniazid	Inhibits essential enzymatic reactions in bacterial cells[69, 83]
Vancomycin	Inhibits bacterial ribonucleic acid synthesis[40] (?)
Erythromycin	Inhibits protein synthesis of bacterial cells[11] (?)
Novobiocin	Increases permeability of bacterial cytoplasmic membrane[12] (?)
Nitrofurans	Inhibit essential enzymatic reactions in bacterial cells[85] (?)
Kanamycin	Unknown
Triacetyloleandomycin	Unknown
Neomycin	Unknown
Ristocetin	Unknown
Colistin	Unknown

* Question mark indicates evidence which is either unconfirmed or appears at present not to be conclusive.

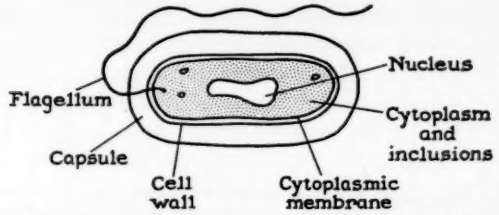

Fig. 1. Diagram of structural relations in bacterial cell. (Reprinted from R. Dubos, ed.: *Bacterial and Mycotic Infections of Man.* J. B. Lippincott Company.)

shown to exert their specific actions upon bacteria: (1) by interfering with the synthesis of the relatively rigid *cell wall* (Fig. 1), which maintains the structural integrity of the bacterial cell;[65] (2) by damaging the delicate *membrane*, which encloses the bacterial cytoplasm and serves as an essential osmotic barrier to the free diffusion of many metabolites;[74] and (3) by blocking *cytoplasmic metabolic reactions* which are involved in critical synthetic processes within the cell.[29]

For an antimicrobial drug to be useful in clinical medicine, its toxicity must obviously be *selective*;[30] i.e. it must not inflict serious damage on the cells of the human host. Thus it may be generally assumed that acceptable antimicrobials act upon metabolic reactions in bacteria which either do not exist or are inaccessible in mammalian cells.

INTERFERENCE WITH SYNTHESIS OF CELL WALL

Since the wall of the bacterial cell differs in chemical composition from the walls or membranes of other cells,[29] it constitutes a potential site for the selective action of antimicrobial drugs. Not all bacteria, however, have cell walls of identical chemical make-up.[51, 65] Walls of gram-negative bacteria, for example, contain 11 to 20 per cent lipid and most, if not all, of the usual amino acids, whereas those of gram-positive bacteria contain only 2 to 4 per cent lipid and on hydrolysis yield fewer amino acids, none of which are aromatic.[65] The carbohydrate constituents of the cell wall matrices also differ.[23]

A chemical component which is common to gram-positive cell walls is a complex polymer composed of glucosamine, N-acetylmuramic acid, D-glutamic acid, alanine and either lysine or diaminopimelic acid.[23, 57, 82] As shown in Figure 2 the ratio of the N-acetylmuramic acid to the peptide in this complex is 1:1.[61] A second main carbohydrate component in the cell walls of gram-positive bacteria is a polymer of ribitol phosphate. When combined with alanine and glucosamine, it is often referred to as "teichoic acid"[6, 62] (Fig. 3).

In 1949 Park and Johnson[60] reported the first evidence of a bio-

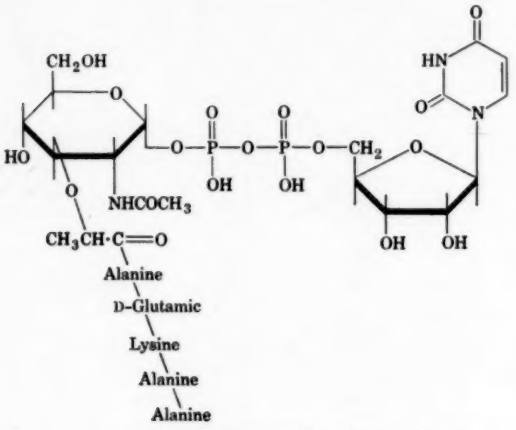

Fig. 2. Muramic acid peptide.

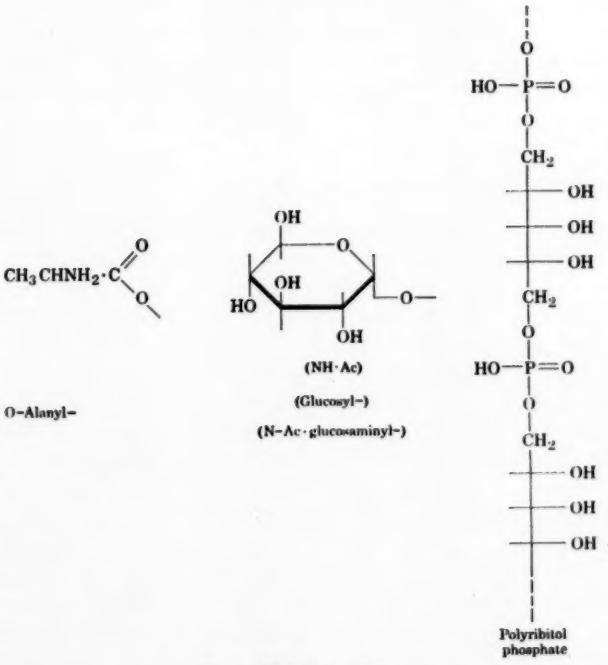

Fig. 3. Teichoic acid.

chemical lesion in bacterial cells treated with penicillin. Hitherto undetected organic phosphate compounds were found to accumulate in *Staphylococcus aureus* cells grown in the presence of penicillin. Three of these were isolated and identified by Park[56, 57, 58] in 1952. All of them contained uridine diphosphate and N-acetylmuramic acid. Their amino acid contents varied: one contained alanine alone, another contained alanine, glutamic acid and lysine. Of particular interest was the fact that the glutamic acid was present as the D-isomer (rare in nature), whereas the alanine existed in both the D and L forms. Finally, in 1957 Park and Strominger[61] discovered that the relative amounts of muramic acid, D-glutamic acid, alanine and lysine which accumulated in staphylococcal cells treated with penicillin were precisely the same as those which exist in the normal cell walls of gram-positive bacteria. The rate of accumulation of the muramic acid compounds indicated that they are involved in a major synthetic reaction of the cells.[61] These findings led to the suggestion that penicillin interferes with the synthesis of the bacterial cell wall and that the organic compounds originally detected by Park and Johnson represent cell wall precursors which accumulate in the treated cells as a result of their failure to be polymerized in the presence of the drug.[51, 61] A year later (1958) Armstrong et al.[15] reported the accumulation of cytidine diphosphate ribitol in penicillin-treated cells, suggesting a similar block in the synthesis of "teichoic acids."

The significance of these biochemical data was revealed in parallel experiments relating to the effects of lysozyme on certain bacterial cells. This enzyme, which is present in egg white, leukocytes, tears, and elsewhere, was found to dissolve the cell walls of susceptible bacteria and thus cause them to lyse.[29] Disruption of the enzyme-treated cells, however, could be prevented by raising the osmotic pressure of the suspending medium to approximately the level of that existing within the bacterial cells. Bacteria thus treated were stripped of their outer cell walls and existed as naked bodies surrounded only by delicate cytoplasmic membranes. These protoplasts (or spheroplasts, as they are called when not all the wall has been removed) behaved essentially like normal cells, except for their exquisite sensitivity to osmotic lysis.[49, 50, 74] In 1956 Lederberg[44] showed that treatment of growing bacterial cells with penicillin in a hypertonic medium results in the formation of protoplasts. When the penicillin was removed from such mixtures, synthesis of the cell walls was resumed and the organisms again began to multiply.

As a result of these observations it is now generally believed that penicillin exerts its bactericidal effect by interfering with the synthesis of the cell walls of susceptible bacteria, thereby converting them to protoplasts, which in turn are destroyed by osmotic lysis.[51, 61, 66] The

recent finding of numerous bacterial protoplasts in the relatively hypertonic urine of patients treated with penicillin appears to add clinical support to this widely accepted hypothesis.[9]

Other effects of penicillin on bacterial metabolism have also been described. Assimilation of amino acids and the formation of the inducible protein enzyme, β-galactosidase, by *Staphylococcus aureus* have been shown to be blocked by the action of penicillin.[13, 22, 33] Since the effects of penicillin on both processes can be prevented by merely protecting the treated cells from osmotic lysis,[36] it is evident that these actions of penicillin are secondary rather than primary. The exact nature of the primary biochemical lesion, which interferes with the synthesis of the essential polymers in the walls of the susceptible cells, is not yet known. Since radioactive penicillin has been found to become fixed to the cytoplasmic membrane,[20] it is possible that the drug acts on a synthetic mechanism located in the membrane and having to do with the formation of the wall. At any rate, the primary lesion, whatever its nature, clearly involves the cell wall. Furthermore, the lesion is usually lethal, provided the organisms are multiplying. If for any reason their metabolism is suppressed to the point at which they are not synthesizing new cell wall, they will not form protoplasts in the presence of the penicillin[44] and, therefore, will not by destroyed by lysis.[18, 79] The clinical significance of this point has been emphasized elsewhere.[70]

As might be expected, other antibiotics have been found to exert similar effects on the cell walls of susceptible bacteria. Bacitracin causes the accumulation of uridine nucleotides in treated cells,[1] and bacitracin and oxamycin both inhibit the incorporation of amino acids into cell wall peptides.[16, 59]

DAMAGE TO CYTOPLASMIC MEMBRANE

The cytoplasmic membranes of bacterial cells have active transport mechanisms which control the assimilation of essential metabolites.[29] In addition, the lipoprotein membranes contain enzymes which may participate in the synthesis of internal proteins[7, 16, 72] as well as in the formation of the cell wall.[21] Moreover, they act as important osmotic barriers which permit the cells to concentrate within their cytoplasms such vital metabolites as purines, pyrimidines, amino acids and organic phosphates.

A number of antimicrobial drugs have been shown to affect the cytoplasmic membrane. Polymyxin, for example, causes sensitive species of gram-negative bacilli to "leak" soluble nucleotides normally held within the cell.[53] The interaction between polymyxin and the membrane is antagonized by metallic ions in such a way as to suggest that the drug combines directly with the lipoprotein.[52]

In keeping with these findings are the convincing photographs of a fluorescent form of polymyxin concentrated in the cytoplasmic membranes of sensitive bacilli.[53]

Streptomycin likewise has been shown to increase the permeability of the cytoplasmic membranes of susceptible gram-negative bacilli.[4, 5, 63, 64] There is also evidence that it inhibits general protein synthesis (*vide infra*).[4, 27, 41] Novobiocin[12] as well as tyrocidine[32] (which is too toxic for tissue cells to be of clinical use, except under special circumstances) likewise damages the osmotic barrier of bacterial cells.

BLOCKING OF CYTOPLASMIC METABOLIC REACTIONS

A number of important antimicrobal drugs appear to act without seriously affecting either the permeability of the cytoplasmic membrane or the formation of the outer cell wall. These may be conveniently divided into two groups: those that inhibit protein synthesis and those that interfere with other cytoplasmic metabolic reactions essential to the bacterial cell. The prototype of the first group is chloramphenicol. Its action has been exhaustively studied by biochemists interested in the mechanisms of protein synthesis.[14, 19, 34, 43, 78]

Current concepts of protein synthesis may be briefly summarized by the following equations:*

$$(1)\quad \mathrm{AA\,\&\,ATP} + \mathrm{E} \rightleftharpoons \mathrm{E-AMP-AA} + \mathrm{PP}$$

$$(2)\quad \mathrm{E-AMP-AA} + \mathrm{S-RNA} \rightleftharpoons \mathrm{S-RNA-AA} + \mathrm{AMP} + \mathrm{E}$$

$$(3)\quad \mathrm{S-RNA-AA} + \mathrm{Rs} \xrightarrow{\mathrm{GTP}} \mathrm{Rs\ protein} + \mathrm{S-RNA}$$

in which *AA* is amino acid, *ATP* adenosine triphosphate, *E* enzyme, *PP* diphosphate, *S-RNA* soluble ribonucleic acid, *Rs* ribosomes containing ribonucleoprotein, and *GTP* guanosine triphosphate. According to these concepts, which are continually being extended and modified,[38, 55, 77] free amino acids in the cell react enzymatically with adenosine triphosphate to form an amino acid-adenosine monophosphate complex. The amino acid thus "activated" is transferred to low molecular weight ribonucleic acid (S-RNA), which in turn transfers the amino acid to high molecular weight ribonucleoprotein (ribosomes), where it is incorporated into protein by a series of as yet unidentified reactions.

Present evidence indicates that chloramphenicol inhibits the synthesis of bacterial protein by blocking the transfer of the S-RNA-amino acid complex to the ribosomes.[28, 42, 72] In other words, it interferes with the reaction represented by equation (3). In keeping with this conclusion is the fact that an "abnormal" RNA, of molecular weight comparable to that of soluble RNA, accumulates in bacterial cells

* Modified from Yarmolinsky and de la Haba.[84]

treated with chloramphenicol.[24, 39, 54] Only the natural D (-) *threo* isomer of chloramphenicol exhibits full biological activity.[35, 48] No effect upon the earlier steps in the synthetic process (equations [1] and [2]) has been demonstrated.

Because protein synthesis is a process common to all living cells, the question may be asked as to why chloramphenicol should exert such a selective action on bacteria.[10] The reason is at present not known. Selectivity may be due either to a special penetrability of bacterial cells to the drug, or to differences in the mechanisms of protein synthesis in different kinds of cells.[30]

The tetracycline antibiotics also inhibit protein synthesis in susceptible species of bacteria.[8, 31, 45] Here again there is an accumulation of abnormal RNA[17] suggestive of a block in reaction (3). In addition, it is known that the tetracyclines have chelating properties[3] and that their bacteriostatic effect may be antagonized by certain divalent cations.[71, 75, 76] Furthermore, Mn^{++} has been found to reverse the inhibitory action of chlortetracycline (Aureomycin) on the nitroreductase activity of *Escherichia coli*.[67, 68] These facts, coupled with (*a*) recent observations on the role of Mg^{++} in binding together the ribonucleoprotein subunits of bacterial ribosomes[26, 43, 73] and (*b*) the finding that chelating agents may inhibit protein synthesis in cell-free systems,[47, 77] suggest the possibility that the chelating properties of the tetracyclines may be related to their ability to inhibit protein synthesis in bacterial cells. There is as yet no direct evidence to support this attractive hypothesis.

Among the antimicrobial drugs which inhibit other cytoplasmic reactions, the sulfonamides have been the most thoroughly studied. As early as 1940 their mode of action was clearly shown by Woods[80] to involve a competitive inhibition of the metabolism of p-aminobenzoic acid.[80] This bacterial metabolite, which is structurally similar to the sulfonamides, was later found to be a constituent of the folic acid vitamins.[81] The drug p-aminosalicylic acid, widely used in the treatment of tuberculosis, likewise competes with p-aminobenzoic acid for enzyme sites involved in folic acid synthesis.[25, 37]

That antibacterial drugs now in use inhibit other essential metabolic reactions of bacterial cells seems almost certain. As indicated in Table 1, however, evidence relating to the precise mechanisms involved is still inconclusive.

SUMMARY

The modes of action of currently useful antibacterial drugs have been briefly reviewed in relation to modern concepts of bacterial metabolism. Present evidence indicates, in general, that those drugs which are

bactericidal (e.g. penicillin, streptomycin, bacitracin and polymyxin) either interfere with the synthesis of the cell walls or injure the cytoplasmic membranes of susceptible bacterial cells, whereas those that are primarily bacteriostatic (chloramphenicol, the tetracyclines, the sulfonamides and p-aminosalicylic acid) tend to inhibit cytoplasmic metabolic reactions essential to growth, including the synthesis of protein.

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PENICILLINS

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The usefulness of penicillin in the treatment of certain infections has not changed in the two decades since Dr. Florey and his colleagues first described its clinical efficacy.[6] Penicillin is by all criteria the best and most potent antimicrobial agent available. Its only deficiencies have been its propensity to be allergenic in a few patients, its rapid excretion through kidney, and its narrow spectrum of antibacterial activity. In the past two years, however, new, partially synthesized variants of the original benzyl penicillin (G) have been prepared. Antimicrobial activities of these are considerably broader, and the indications for prescription of penicillin thus have been extended to include treatment of some infections in which penicillin G has been ineffective. It can be presumed that future penicillins will have an even more widespread utility. It seems appropriate, consequently, to review some of the pharmacologic activities of these new preparations and to compare them with those of penicillin G so that their administration to human beings can be done properly.

CHEMISTRIES OF PENICILLINS

Benzyl penicillin (G) is produced solely by fermentation (Fig. 4). Between 1948 and 1958 a number of chemical modifications of the initial soluble penicillin salt were prepared, each of which altered to some degree the pharmacologic properties of penicillin G in the human patient. These included production of insoluble salts such as procaine penicillin (1948) and benzathine penicillin (1951).[10, 12] Each, by interfering with rapid absorption from an intramuscular depot, permitted continuing, though low, levels of penicillin in blood for periods ranging from one day (procaine) to 21 days (benzathine) rather than the few hours of measurable serum levels provided by the sodium or potassium salt. Penicillin G was also combined with probenecid

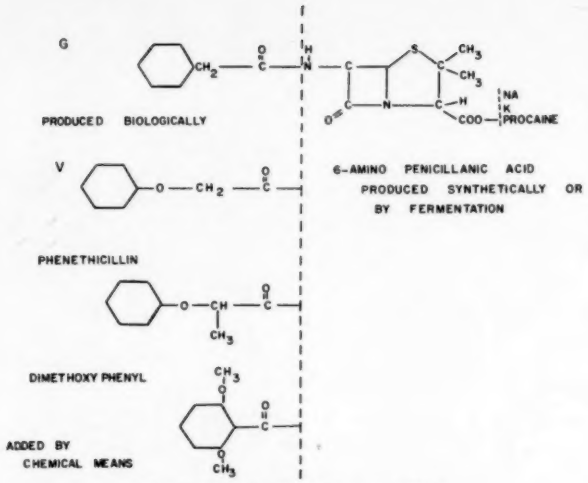

Fig. 4. Chemistries of the penicillins.

(1951), a chemical which competes with penicillin's transport across the kidney tubule.[4] With its combination penicillin in serum persisted at peak levels, thereby necessitating fewer doses per day of either an oral or parenteral preparation.

These two kinds of penicillin G still have merit in present medical practice. Note, however, that delaying absorption by a different salt of penicillin G or interfering with its excretion does not alter its antimicrobial activity, nor its potential in producing hypersensitivity phenomena. Indeed, until the advent of newer preparations of penicillin the efficacy and toxicity of all preparations of penicillin were essentially the same; only their dosage differed, and this mainly in the number of doses needed daily.

In 1955, with penicillin G as the precursor, a new kind of penicillin was described whose inherent physical and pharmacologic properties differed somewhat from the parent substance (Fig. 4).[13] Alpha phenoxymethyl penicillin (V) is stable in an acid medium and, because of its easy conversion into soluble alkaline salt at the expected pH of the duodenal content, measurably improved intestinal absorption occurs. As a result the oral use of penicillin V became a dependable method to administer the agent and was the first real change in pharmacologic properties of penicillin G despite the fact that in most other respects it simulated G. After its introduction the oral route of administering penicillin was used more commonly, and rightfully so.

Some time after the demonstration that 6-amino penicillanic acid (APA) could be synthesized (1958), evidence became available that

the same parent chemical could be produced biologically—the fermentation process being stopped short of the eventual formation of benzyl penicillin (Fig. 4).[3] With the antimicrobially inert 6-APA nucleus chemists have elaborated a series of new penicillins, some of whose chemical properties are appreciably different from those of penicillin G.[11] The differences include the observation that one, alpha phenoxyethyl penicillin or phenethicillin (Fig. 4),[14] is as acid-stable as penicillin V, albeit not as antimicrobially active on a milligram basis. Another, dimethoxyphenyl penicillin, has the ability to bypass the penicillin-neutralizing properties of penicillinase (Fig. 4).[5] Others are being developed which are active against certain gram-negative organisms, and still others will have both the chemical facility to bypass penicillinase, and a molecule which is absorbed freely from the intestinal tract, and thus can be given orally.

PEDIATRIC VERSUS ADULT DOSAGE SCHEDULES*

Despite the obvious fact that most chemicals are prescribed according to body size, or weight or body surface, commonly used dosage schedules for penicillin G and all its derivatives, including penicillin V, are essentially the same for adults and children of all sizes and weights. Presumably, this clinical habit has resulted because penicillin produces no tissue toxicity, and dosages need not be kept at the minimal inhibiting levels necessary to control spread of infection; nor are they. Nevertheless such empiric prescriptions of penicillin in pediatrics are not necessarily appropriate.

When absorbed into serum, each penicillin is excreted largely through the kidney, and the renal clearance is approximately equivalent to the total renal plasma flow.[1, 2, 8] Hence 60 per cent of that in plasma is excreted within an hour, and the remainder leaves the blood at a proportional rate thereafter. Furthermore, the clearance is independent of height of blood level of penicillin and of rate of urine flow. Twenty per cent is eliminated by glomerular filtration, the remainder by tubular secretion. These clearance values are, of course, lower in infants before the sixth month because of immature kidney function. As effective renal plasma flow is closely related to surface area, dosage of penicillin can be calculated most logically by estimating that area (nomogram of DuBois).

The average adult has approximately 1.7 square meters of body surface, a 9-year-old child has 1.0, and a 2-year-old has 0.6 square meter. Thus as there is more area per unit mass in children than in adults, more penicillin is needed per weight; i.e. the dose per pound of body

* Material in a pertinent editorial appeared too late for inclusion in this text. See A. J. Glazko: *Pediatrics*, 27:503–506, 1961.

weight is commensurately greater in children. In using the foregoing example of the 3 surface areas, and considering an infection caused by a highly susceptible organism such as group A beta hemolytic streptococci, about 300,000 units of penicillin per 24 hours per square meter of body surface is ideal dosage. An adult would need 500,000 units, a 9-year-old boy 300,000 units, and a 2-year-old child 180,000 units. In general the child of 7 to 9 years needs *one third to 60 per cent less* than the adult dose, and the infant under 6 months of age only *one tenth* the adult dose.

By another and simpler method the same conclusion can be fashioned. Because concentration of penicillin in blood is dependent upon size of dose and total fluid volume, children require smaller doses than adults to attain any desired blood concentration, for their fluid volume is less. But since there is no nomogram to compute extracellular fluid volume by age or size, dosage requirements can only be approximated. But smaller patients need less penicillin than larger people to achieve a desired therapeutic level.

After 20 years the common practice of prescribing adult-sized doses of penicillin to children is not likely to change, nor perhaps is it practicable to make the suggestion now that it should change for penicillin G. But the recommendation surely applies to the new penicillins. With some, more is needed in grams to achieve the desired effect, and expense is a real problem, for some are 10 to 20 times more costly than penicillin G.

PHARMACOLOGIC PROPERTIES

Distribution into Body Fluids and Tissues

An axiom in therapy of infections is that for maximal effect the antimicrobial agent must be available at and in the area of inflammation so that intimate and continuing drug-organism exposure is maintained.[16] Implicit in this concept is that the concentration of the drug must be higher than the measured level of susceptibility of the microorganism in vitro for the majority of the hours each day. The therapeutic efficacy of penicillin is dependent mainly upon its total aggregate time at the focus of infection in effectual concentrations.[9] As tissue concentration persists for approximately the time the drug is measurable in serum, presumably some knowledge of serum levels is essential for sensible regimenting of the drug to the patient. Unfortunately, perhaps, penicillin does not penetrate some tissues to the same extent as others, so that there can be no general rule of prescription to achieve the desired serum level and thus also the correct tissue concentration. For example, amounts of penicillin reaching normal muscle, including the heart, the

mucous membranes of the throat, and the central nervous system are from fivefold to tenfold less than those in intestine or kidney or lung after a single dose (Table 2). Thus it is almost impossible, with any of the penicillin G products, to eradicate streptococci from the throats of carriers, or to treat meningitis or endocarditis, without raising the dose considerably to accommodate for the individual tissue barrier.

Similarly, abnormal inflammatory tissue may compromise penetration of penicillin into them. Concentrations in the shaggy, avascular vegetations of endocarditis, the thick walls of an abscess, or lesions in bone associated with thrombosis of end arteries, are inevitably less than those in acute inflammatory areas. These diseases and others too need to be recognized by the physician so that he may provide enough added

TABLE 2. *Relative Tissue Distribution of Penicillin, 2–3 Hours and 4–6 Hours after a Single Parenteral Dose*

	2–3 HOURS	4–6 HOURS
Blood	4	1
Kidney	4	1
Intestinal wall	3	Trace
Lung—normal	3	Trace
With pneumonia	4	1
With fibrosis	1–2	0
Skin and mucous membranes	3	0
Liver and spleen	3	Trace
Muscle	2	0
Heart	1.5	0
Central nervous system	<.5	0
Bone (including marrow)	<.1	0

penicillin to permit maximal killing effect upon pathogenic microorganisms located in areas difficult to get at.

Routes of Administration

Penicillins are reasonably innocuous chemicals as evidenced by the fact that in crystalline form all of them can be given by any route to the human being—local, oral, parenteral, intravenous or directly into body spaces, e.g. joints, pleural space, intrathecally or intraperitoneally. Absorption into blood, and thus into tissues, via these routes is not, however, identical (Table 3). After a parenteral or intravenous dose, absorption is almost complete, and most of the dose (60 to 90 per cent) can be recovered in urine. With orally administered penicillin G or V and phenethicillin, between 15 and 40 per cent of a single dose is excreted, indicating that the absorption defect is considerable.[11, 14, 15] Accordingly, if penicillin G is the preferred agent, between three and five times more drug must be given orally to attain levels similar to

those with a parenteral dose. With penicillin V and phenethicillin the discrepancy is less, but at least 20 per cent more of either must be given to be equivalent to an intramuscular dose.

Concomitant ingestion of food interferes with absorption of all penicillins; thus the required multiple daily doses should be arranged so that each is given at least 45 minutes before or after food. The defect in intestinal absorption is not due to acid content of the stomach.[15] Rather, the chemical is absorbed only in a small segment of the duodenum—not at all in the jejunum, ileum or colon. Efforts to enlarge this narrow zone of absorption have to date been unsuccessful. The moderate advantages of penicillin V and phenethicillin are due only to their stability and solubility in the alkaline medium of the duodenum; the area of their absorption has not been improved over that of penicillin G.

Dimethoxyphenyl penicillin is not absorbed from the gastrointestinal

TABLE 3. *Relative Degrees of Absorption of Penicillin into Blood from Various Depots*

ROUTE*	G	V	PHENETHICILLIN	DIMETHOXYPHENYL PEN.
Intramuscular	90+%	—	—	50–60%
Intravenous	100%	—	—	100 %
Oral (GI absorption)	20%	35–40%	35%	—
Intrathecal	100%	—	—	?
Intraperitoneal	100%	—	—	50 %
Intrathoracic	100%	—	—	50 %
Joints	60% (?)	—	—	30 %
Saliva	0	0	0	0

* Preferred or only route of administration.

tract and must therefore be administered by other routes. Newer preparations will probably be like penicillins G and V, but precise descriptions of their properties must await further studies.

The oral route of administering penicillin should be used only in patients whose entire gastrointestinal tract is functioning reasonably normally. No absorption takes place from either a paralyzed gut or one which is overactive.

Local instillation of various penicillins directly into body spaces is safe, although not often necessary. Only in instances in which adequate concentrations cannot be attained from blood levels because of tissue barriers is local use recommended, and then only as an adjunct to the preferred route of administration. Occasionally the thick, fibrinous exudates of gonorrheal inflammation in joints or pneumococcal pleuritis and pus formation require that extra amounts of a penicillin be deposited in the area. Dosage in these cases is dependent upon size of space and the amount of fluid in it. Rarely is more than 5 units of

penicillin per unit of fluid needed. For example, in a 500-cc. pleural empyema, no more than 2500 units of penicillin need be instilled irrespective of the amount of diluent used to put it in. As is true with penicillin's prescription in general, it is common habit to use much more than this; the point is that *this excess is not necessary*.

Injection of a penicillin into intrathecal space is virtually never required for treatment of nervous system infection despite the fact that amounts in excess of 500 mg. are not particularly irritating to its delicate membranes, inflamed or not. It is illogical to presume that distribution of the agent into all segments of the central nervous system can be achieved when there is inflammation which may, and often does, block circulation of spinal fluid, and this same phenomenon applies equally to other body spaces. Whenever the exception is made, however, penicillin must be given by some fashion which assures proper blood concentration. To secure proper concentration in the nervous system, daily doses far in excess of 5,000,000 units must be given parenterally. Such large amounts overcome the blood-brain barrier and secure

TABLE 4. *Infections in Which Penicillin G in Large Doses, with or without Combination with Streptomycin, Is Recommended*

Certain nongroup A streptococci, e.g. enterococci, fecal streptococci
Klebsiella
Actinomyces, particularly genus nocardia
Species of Proteus
Some strains of *Hemophilus influenzae* and pertussis
Listeria, erysipelothrix

even distribution of drug into all segments of the central nervous system.

There is another reason why local use of a penicillin is to be avoided. Generally an impressive increase in allergic reactions follows, and this is true particularly with troches, lozenges, pastes and other ointments.[20]

In certain, fortunately few, infections massive amounts of penicillin are needed. When the infecting microorganisms are inhibited by amounts in excess of 2 units of penicillin or when tissue barriers interfere with penetration of drug into the infected area, the recommended dose of penicillin G is 10,000,000 or more units daily, parenterally. Infections such as those caused by fecal streptococci (peritonitis, endocarditis) or Klebsiella (pneumonia), which are partially resistant, or meningitis due to the pneumococcus or meningococcus, into which area penicillin passes poorly, are classic examples of these states (Table 4). The drug in huge amounts can be given by the intravenous route, by intermittent intramuscular injections or by continuous subcutaneous clysis. Although there really is no limit to the amount of penicillin

which can be administered safely, all preparations are either a sodium or potassium salt. When 50 gm. or so is given, toxicity from the cation has been observed; thus the limiting factor to total dose, irrespective of kind of penicillin, has nothing to do with antimicrobial activity. One gram of penicillin G (1,667,000 units) or dimethoxyphenyl penicillin contains approximately 2.5 milliequivalents of potassium or sodium.

Toxicity

Hypersensitivity phenomena inevitably occur when any foreign substance is administered to the human being and penicillin does occasion reactions in a small percentage of recipients.[20] Once absorbed into blood, about 30 per cent of the chemical binds with protein, thus forming a potential allergen. Reactions are like any allergy, ranging from simple delayed skin eruptions through the more serious delayed anaphylaxis with, occasionally, permanent defects from serum sickness, to the abrupt and morbid acute anaphylaxis. Reactions occur after any route of administration, although the more serious forms are less often expected with the oral route. Reviews of these events, descriptions of their clinical characteristics, their incidence in any population group and their management have been described often and accurately. There is no sensible purpose in another review except to emphasize that a good history is the best preventive.

There seems to be no cogent reason to believe that the newer, partially synthesized penicillins will be free of a similar kind of allergenic potential. Indeed, each of them binds with plasma protein to a degree like that of penicillin G or its various derivatives. In a recent symposium about dimethoxyphenyl penicillin, which summarizes initial experiences in about 500 patients receiving it, minor allergic phenomena were noted in less than 3 per cent of the patients.[18] This is an acceptably low figure.

What is of interest, though, is the possible lack of cross sensitization among the various new and old penicillins. Although the work so far described with the newer synthetic ones is inadequate and more is surely warranted, some facts are available for interpretation.[17] In a few patients studied who were allergic to penicillins G and V, as evidenced both by presence of hemagglutinating antibodies and by overt skin reactions, antibodies to dimethoxyphenyl penicillin were absent. Further, these patients tolerated continuing doses of the new agent without exhibiting untoward reactions of any order. Similarly, in a few patients actually having an acute delayed anaphylaxis due to penicillin G, dimethoxyphenyl penicillin was given and the reactions disappeared on schedule, and no others occurred. Studies with antibodies have also

shown that dimethoxyphenyl penicillin did not interfere with the reaction between red cells coated with G and the patient's serum, but excess penicillin G would block the reaction between serum and red blood cell coated with G. The evidence is highly suggestive at least that there is immunologic distinction between the two penicillins despite the fact that their modes of action are probably similar.

New penicillins may excite other kinds of untoward reactions not yet reported. Among these is their presumed ability so to alter normal microbial flora in respiratory and intestinal tract that superinfections may be excited. Until the fact is observed, however, restrictions in use need be no different from those now practiced with penicillin G or V.

Other Pharmacologic and Microbiologic Differences and Similarities between Penicillin G and Partially Synthesized Penicillin

Dimethoxyphenyl penicillin has important differences in a number of properties from those of penicillins G and V.[17, 18, 21] Most important among these is that, on a weight basis, against susceptible strains about 20 times more synthetic penicillin is required for maximal killing. This is evident in the management of infections caused by staphylococci, pneumococci and other penicillin-susceptible species. For this reason the agent cannot be considered a substitute for penicillin G or V, except in instances of unusually severe reactions to the latter drugs. When used in proper amounts, however, dimethoxyphenyl penicillin is as efficacious a bactericidal agent as penicillins G and V. On the other hand, because dimethoxyphenyl penicillin's antibacterial activity is not neutralized by the presence of penicillinase, it is the drug of choice in staphylococcal disease in which the organisms are producing that enzyme.

A second difference also has an important clinical implication. In the management of a few infections, notably enterococcal or fecal streptococcal infections, a combination of penicillin G and streptomycin exerts a synergistic effect. The combination may also be effective in infections due to proteus, Hemophilus and Klebsiella (Table 4). There is as yet no evidence that a combination of dimethoxyphenyl penicillin with any other antimicrobial agent, including streptomycin, has any effect upon its basic antibacterial activity. The only recommendation possible from the data available is that the new penicillin should be given alone, unless, of course, a multibacterial infection deserves therapy.

Finally, there is evidence that when diluted in commonly used intravenous solutions, dimethoxyphenyl penicillin may lose potency after 8 to 12 hours. Penicillin G in solution is stable for days. The decay of dimethoxyphenyl penicillin also occurs in diagnostic disks kept at room

temperature—a feature which becomes important when sensitivity testing is done.

The emergence of organisms resistant to penicillin G has not been observed; the same statement applies to dimethoxyphenyl penicillin. Further, *staphylococci do not emerge resistant to penicillin*. The penicillinase which they elaborate is an inherent metabolic process, and it is this enzyme which prevents effective use of penicillin G against most strains. Enzyme production is not a result of any genetic alteration, and so-called resistance is strictly a function of penicillinase production by staphylococci.

A second and intriguing similarity between the new penicillins is that their minimal inhibiting concentration wth any bacterial species and the maximal killing activity are essentially identical. This apparently is true irrespective of the technique used to measure these activities or the number of organisms used in the test. For example, all strains of staphylococci, and in numbers ranging from 10^{-2} to 10^{-8} dilutions, are killed by concentrations of dimethoxyphenyl penicillin between 1.56 and 6.25 micrograms per milliliter. The same remarkably small difference is noted with penicillin G's activity upon nonpenicillinase-producing strains.

Finally, distributions of the two kinds of penicillin into various body fluids and tissues follows virtually identical patterns, and their excretions are similarly alike through kidneys.

These similarities and differences require careful scrutiny prior to the wise prescription of either agent. The crucial difference is that penicillin G is given in units, penicillin V and phenethicillin in milligrams, and the new synthetic penicillins, beginning with dimethoxyphenyl penicillin, in grams. One thousand units of penicillin G is equivalent to 0.6 mg., and since the usual daily amount is less than 2,000,000 units parenterally, only a gram is needed. On the other hand, daily doses of penicillin V or phenethicillin in children should not be less than 250 mg. 4 times daily orally, and more is needed unless the infection is superficial and acute and the organisms are exquisitely susceptible to penicillin. In contrast, the minimal amount of dimethoxyphenyl penicillin is 4 gm. daily, and more is recommended for serious staphylococcal disease, which is uniformly associated with tissue destruction and pus.

DESIGN OF A THERAPEUTIC REGIMEN, WITH PARTICULAR REFERENCE TO DIMETHOXYPHENYL PENICILLIN

Penicillin is now the drug of choice for all infections caused by the microorganisms listed in Table 5. It is also efficacious in infections caused by more resistant organisms (Table 4). In adults with infec-

TABLE 5. *Infections in Which Penicillin G is Drug of Choice*

All strains and species of streptococcus
Pneumococci
Nonpenicillinase-producing strains of staphylococcus
Gonococcus
Spirochetes, Borrelia and spiral organisms of mouth
The Clostridia, Cornybacterium and Anthrax

tions caused by the susceptible organisms, oral doses of penicillin V and phenethicillin in the range between 1 and 1.5 gm. daily are sufficient, and somewhat less if penicillin G is given parenterally (Table 6). Larger amounts are needed when the infecting bacteria are resistant to more than 1 microgram of penicillin per milliliter, and doses of 10,000,000 or more units are needed in cases caused by organisms resistant to more than 3.5 units per milliliter. These amounts are given without event, albeit with some discomfort to the patient and inconvenience for the physician. Similar large amounts are required when

TABLE 6. *Susceptibility of Common Pathogens to Penicillins*

	PENICILLIN G UNITS/ML.	DIMETHOXYPHENYL PENICILLIN MCG./ML.
Group A streptococci	0.016	0.3
Pneumococci	0.016	0.3
Gonococci	0.016	0.3
Meningococci	0.016	0.3
Nongroup A streptococci		
Viridans	0.05–0.5	0.02–5.0
Fecal	2.5–3	3.–10
Staphylococci (nonpenicillinase producing)	0.06	2.–6
Staphylococci (penicillinase producing)	100.	2.–6.
Klebsiella pneumoniae	12.5	12.5–400
Proteus vulgaris	0.4–4.	6.25

A single intramuscular dose of 300,000 units of aqueous penicillin produces a peak level in blood of more than 5 mcg./ml. Levels above 0.05 mcg. persist for 4–5 hours. Procaine penicillin in the same amount produces levels of about 0.05 mcg./ml. for 18 hours. See text for levels after a dose of dimethoxyphenyl penicillin.

there is a problem of distribution of penicillin into a specific lesion. For instance, penicillin is adequate therapy for meningococcal disease—the organisms are exquisitely susceptible. When the infection is located in the central nervous system, large doses of penicillin are required, for the blood-brain barrier to penicillin is of high order. Sulfonamides are also extremely active against the meningococci, but they traverse the blood-brain barrier in excellent fashion. Therefore sulfonamides are the drug of choice for meningococcal meningitis. Therapy with them is no more effective than with penicillin, but manifestly they are simpler to administer.

Dimethoxyphenyl penicillin is the drug of choice mainly for severe infection caused by penicillinase-producing staphylococci (thus all "resistant" strains).[5]

None of the penicillins, however, are effective in the management of viral or fungal infections except those caused by nocardia. The large group of enteric gram-negative bacilli similarly are unaffected by penicillin except in impractically large amounts. In the very near future, on the other hand, new partially synthesized preparations of penicillin may well have activity against most of these.

Thus eventually, and probably within the year, some brand of penicillin will be the drug of choice for every bacterial disease common to man. And this is good, for penicillin is the best agent in ease of administration, safety, and speed and degree of killing activity.

Infections are treated most successfully when the invading pathogenic organisms are both prevented from multiplying and are killed. As pointed out, this can be achieved by maintaining concentrations of the antagonist at the site of inflammation for the majority of hours each day. The "majority of hours" deserves qualification, however, for 24-hour exposure is not needed when the site of inflammation has adequate vascular supply.[19] After exposure to a killing agent there remain residual viable bacterial cells; approximately 99.99 per cent of a susceptible organism such as pneumococcus are eradicated. The remainder are not dead and, although incapable of causing further infection when the antagonist is present, are potentially able to revive. These inevitably must be sterilized by body defenses—not by drugs—or the infection is never cured. After cessation of exposure to the antagonist the residual bacteria eventually rejuvenate and begin again to multiply. This so-called lag phase, drug induced, persists for varying numbers of hours—in the instance of staphylococci, two or three; of pneumococci, perhaps as long as six to seven hours. During the lag period penicillin has no activity and need not be present for its maximal killing effect because the infection is not spreading. Before the bacteria reach the stage of logarithmic growth, however, a priming dose is necessary. Thus, in design of an effective therapeutic regimen there can be, in most infections, a short number of hours between doses in which there is no detectable penicillin in serum. For example, in pneumococcal pneumonia 500,00 units of penicillin G or 400 mg. of penicillin V or phenethicillin, given every 8 hours, is good therapy. Penicillin persists four to five hours; there follows the lag phase for a minimum of five hours. A repeat dose every eight hours prevents pneumococci from attaining their logarithmic growth phase, and thus the infection is contained until the body can take over the mopping-up procedure.

Discontinuous therapy, on the other hand, is not always proper and wise. In infections such as osteomyelitis, exposure of drug to organism

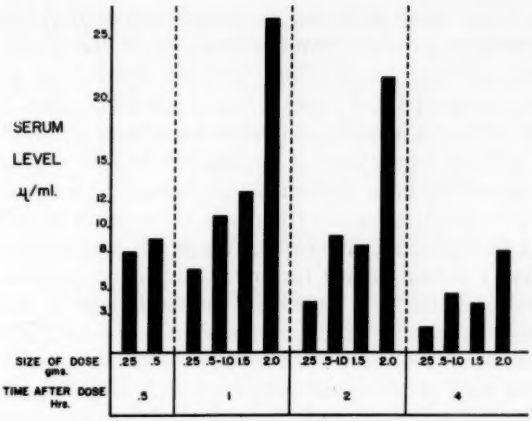

Fig. 5. Blood levels after single intramuscular doses of dimethoxyphenyl penicillin. (From P. A. Bunn and R. Knight: *New York State J. Med.*, Vol. 60.)

is compromised by a variety of events, including the difficulty of penetration of drug into the avascular destroyed bone. Continuous maintenance of effective levels is thus safer in this instance, for the total aggregate time of exposure which follows any single dose of drug cannot be predicted precisely. Again the physician is responsible for the decision about the spacing of individual doses. If there is any question about which is best for a particular kind of infection, its location, blood supply, or speed of recovery of an organism after exposure to penicillin, administration of drug to provide continuously effective, or more, concentrations of penicillin in serum is highly recommended.

As textbooks of pediatrics and medicine define regimens of treatment adequate for most of the infections listed, it is unnecessary to reiterate these recipes for use of penicillin G or V or phenethicillin (Table 4). To be sure, the programs describe a single dosage schedule for all people irrespective of age or size, but little fault can be found with the safety of these large—unnecessarily large—amounts generally recommended.

Dosage regimens for dimethoxyphenyl penicillin are, however, less well publicized and deserve some definition here. Methods to arrange programs of therapy are applicable to any antimicrobial agent, including all penicillins. Details are warranted because this new penicillin is active against staphylococci which are penicillinase producing, both as prime therapy of infections and for prophylactic reasons. Because it is considerably less potent on weight basis than penicillin G or V, and because it is more costly, care in design is encouraged, a statement which should be implicit in any prescription.

After a single dose of 1 gm. of dimethoxyphenyl penicillin given intramuscularly to an adult, levels in excess of 10 micrograms per milliliter are attained in serum, and concentrations above 5 mg. per milliliter persist for 4 hours (Fig. 5).[4, 5, 17, 18] A single 2-gm. dose raises these amounts in serum appreciably, the peak being over 20 micrograms per milliliter, and the 4-hour level is approximately 8 micrograms per milliliter. As essentially every strain of staphylococci so far studied (many thousands) is sensitive to less than 6.25 micrograms of DMOPP per milliliter, a therapeutic regimen which includes a single gram dose given every 4 hours should suffice for most infections, provided that the area of inflammation is a superficial one and there is no barrier to penetration of drug into it. Unfortunately, many staphylococcal diseases, particularly the most morbid kinds, such as pneumonia, endocarditis and osteomyelitis, are associated with tissue destruction and avascularity. Therefore amounts larger than 6 gm. a day are required.

These dosage recommendations are designed for adults, and for practical purposes include approximately 15 to 20 mg. per kilogram of body weight per day. Obviously, somewhat less is needed for children. According to the work of Day et al.,[7] single doses of 25 mg. per kilogram produce levels at the peak period in excess of 15 micrograms per milliliter, and concentrations above 3 are maintained for more than 3 hours. Thus, depending upon size of the child, single doses of 500 to 750 mg. can be given safely every 4 hours to achieve results expected with 1- to 2-gm. doses in the adult. Because the drug is a costly one, the use of these smaller amounts is of some importance, both economically and academically.

The concomitant use of probenecid, 0.5 gm. twice daily orally, elevates and prolongs blood levels by delaying the excretion of dimethoxyphenyl penicillin. As is true with penicillin G, probenicid delays tubular secretion by interfering with its transport across that membrane. Less probenicid is needed to achieve this effect in children, and doses between 0.25 and 0.30 gm. should suffice. When it is used, dosage of penicillin can be reduced by at least one third. Note, however, that *probenicid's main usefulness is in the patient in whom massive therapy is needed*, e.g. osteomyelitis or endocarditis, and not in the patient who requires only an average prescription. Certain side effects from probenicid preclude its routine use.

Dimethoxyphenyl penicillin also does not penetrate into the central nervous system well; the blood-brain barrier is appreciable. Thus, in the management of a patient with meningitis or intracranial or spinal abscess due to staphylococci, daily dosage in children should exceed 10 gm. daily, and if deemed advisable, the material can be given intrathecally. Doses of 250 to 1000 mg., although irritating, are safe. Local instillation into peritoneum, pleura or joint space can be done safely

TABLE 7. *Causes of Treatment Failure with Penicillin*

1. Wrong choice of drug or delay in initial dose
2. Wrong dose of drug and inadequate duration of therapy
3. Inadequate adjunctive therapy, e.g. incision and drainage
4. Inadequate penetration of drug into lesion because of some inflammatory or physiologic barrier
5. Inefficient host defense response or fatal associated disease process
6. Plateau growth of pathogenic microbes (penicillin acts only on multiplying cells)
7. Onset of superinfection by microbe unresponsive to penicillin

also, although there are few indications for use of these routes of administration.

The only and singular weakness in therapy with dimethoxyphenyl penicillin is the necessity of administering it in large amounts, frequently parenterally. Although it is no more irritating than penicillin G, the patient's sense of humor runs short after a few days of repeated needling. It can be given by subcutaneous clysis and by intravenous drip, but these do not really reduce the troublesome aspects of its use in sick people. It is, though, a remarkable drug with tremendous activity against every strain of staphylococci which produce penicillinase and is clearly the drug of choice in serious infections caused by them. Its judicious use will salvage tissue and life impressively, better than any other antimicrobial agent singly or in any combination. It is anticipated that future penicillins will be equally effective and administrable by mouth.

CAUSES OF TREATMENT FAILURES WITH PENICILLIN

Evaluation of treatment results with penicillin exacts scrupulous inquiry. The penicillins, like other antimicrobial agents, act solely upon the infecting microbe, they have no influence upon inflammation. Successful therapy, then, is as dependent upon what the infected host does with the tissue damage of the infection and the disposal of residual organisms as it is upon reduction of bacterial population by drug therein. If the patient cannot or does not reduce or resolve the inflammation, failure of treatment does not represent weakness of the drug. And not infrequently, despite an ideal dosage regimen of a penicillin, treatment failures occur. Generally the host is at fault—he mobilizes ineffective defenses or reparative processes, and in such instances no amount of added penicillin will alter the unfavorable course of the disease. Table 7 lists certain causes for treatment failures, most of which are self-explanatory.

Penicillins now available act upon a limited number of microorganisms even though this restricted number causes a majority of bac-

terial infections. The physician must be precise in his choice of drug to use for any infection by recognition of the offending bacteria. Too often this precision is lacking—this is not an inherent weakness of a penicillin when there is a treatment failure.

Similarly, the patient deserves prompt therapy given for that period of time required for him to reorganize his defenses in order that they, not the drug, finally eradicate the disease. Duration of therapy cannot be defined for every infection. Again clinical judgment is demanded. Fortunately, the error is frequently made in offering the patient too generous amounts of penicillin for too long. Nevertheless the opposite obtains frequently enough to list it as a cause of treatment failure. For instance, in chronic infections such as endocarditis and meningitis, treatment must be extended two or more weeks; less is hazardous.

Finally, patients treated for a specific infection with penicillin on occasion acquire, prior to complete control of that infection or shortly thereafter, a second infection caused by another microbe. The appearance of a superinfection is not necessarily a treatment failure. Presumably it can be expected any time when a powerful antimicrobial agent with a narrow spectrum of activity is given to a patient highly susceptible to continuing infection. The appearance of a contaminating organism suggests that the first drug has been so powerful that the initial offending pathogens were eradicated before the body had time to repair the anatomic damage to the area. This then remains a healthy spot for infection by another variety of bacteria.

PROPHYLACTIC USE OF PENICILLINS

The use of any chemical to prevent securely an infectious disease can be treacherous despite the fact that prevention of infection is the *sine qua non* of its eradication. Penicillin can prevent infection in only certain limited ways; it cannot be considered in any sense the complete prophylactic. It is not, nor is any antimicrobial agent, as effective as specific biologicals and with rare exceptions is useful generally only on a temporary arrangement.

Many have clearly demonstrated that the use of any form of penicillin can prevent recurrences of streptococcal disease, and benzathine penicillin given once monthly is used most commonly. Even with this classic instance of the preventive usefulness of penicillin, many remain skeptical that in the long range the effort is effective. There are other untoward side effects of its prolonged use that militate against at least some of its benefits.

With individual doses other infections can also be prevented by proper administration of penicillin. Gonococcal and syphilitic infections are examples of this. Similarly, in times of outbreaks of other specific

infections the timely use of penicillin can prevent disease in susceptibles upon exposure, meningococcal disease and diphtheria being the two in which it has a place. Also, penicillin can be given to patients heavily burned or traumatized, perhaps with other agents, to prevent an anticipated superinfection. A list of these possible uses would be legion, including its too common administration as preoperative prophylaxis, but description of these many situations is impracticable; each physician must devise his own program for individual problems.

Two recent studies with dimethoxyphenyl penicillin do require description, however. In Day's study[7] single doses of 125 or 250 mg. were given newborn infants in a hospital nursery. Noses and umbilical stumps were then cultured periodically, and an equal number of infants were observed and studied, but not given the drug. Fewer infants (8.5 versus 38 per cent) failed to demonstrate colonization of staphylococci in either area (the figure is statistically significant). Clearly, colonization with staphylococci was delayed by a single dose of drug, but it was equally true that the protective effect wore off after the fourth day and an additional dose was required if umbilical stumps and noses were to be kept clear of staphylococci during the usual four- to five-day stay in the hospital after birth. In the group receiving dimethoxyphenyl penicillin both body areas became colonized with various gram-negative bacteria.

In the other study nasal carriers of staphylococci were given 1 gm. of dimethoxyphenyl penicillin every 6 hours.[21] Within days the carrier rate fell from 100 per cent to zero. Other organisms in noses and throats were not appreciably altered. No other drug has been shown to change the nasal flora of the carrier of staphylococci.

The implications to be derived from these studies in prophylaxis are far reaching, but before they are accepted at face value, other facets of the problem deserve investigation. For example, noses and umbilical stumps can apparently be kept free of potentially hazardous staphylococci, but it is highly unlikely that they will remain sterile. Perhaps another microbe will eventuate which can cause even worse disease. Obviously at times of outbreaks of staphylococcal disease, particularly in hospitals, the wise use of dimethoxyphenyl penicillin can be expected to break the epidemic, but in the long range the drug will not eradicate staphylococci from our society, hospital or other.

Dosages of any penicillin required to prevent an infection are appreciably less than those justified to treat an established infection. Only small amounts are needed to keep an organism in the resting state, and when they are not multiplying rapidly, there is no invasion or infection. Thus in single circumstances doses of a long-acting preparation, such as procaine penicillin or benzathine penicillin,

which provide the patient with prolonged, low levels of penicillin are adequate preventives—and they can be given at little expense or pain to the patient.

Finally, penicillin does not eradicate disease irrespective of how it is administered or for how long. It would be presumptuous to place any segment of the population upon a long-term prophylactic regimen with the hope that there would follow a significant reduction in the total number of infections in our society. Indeed, the opposite might well obtain: there would be increased numbers of infections caused by microbes insusceptible to penicillin—breeds which conceivably would be difficult to treat with present chemicals. Complete and long-term prophylaxis is impracticable, but a single infection of dangerous import can be avoided for a limited period. Therein rests penicillin's place as a preventive. No one should aim for a germ-free society—this would lead to more troubles than isolated infections in each of us. Most of us choose to reside with microbes.

SUMMARY

Penicillin is the best antimicrobial agent available for the treatment of the vast majority of infections in our society. It kills susceptible microbes faster and it kills more of a single population of bacteria in vivo or in vitro than any other chemical or biological agent alone or in any known combination with other agents. There are now multiple preparations for its easier administration in any kind of infection in any kind of person from his first to his last day. Generally, organisms do not become resistant to frequent exposure to penicillin, and the amount of tissue toxicity which its use involves is remarkably small. Even the uncommon allergic phenomena which it can cause are controllable with accessory agents. There can be no justification whatever for withholding a penicillin if the proper indications for its use exist.

The reason for this long correspondence about old and new penicillins is solely to describe certain of their properties which may change beneficially a common prescription. Indeed, there really can be no single regimen, for infections vary sufficiently in intensity of inflammation to alter the needed concentration of drug necessary to inhibit maximally the pathogenic bacteria therein.

No effort has been made to describe certain events in the human being himself which conceivably play significant roles in his response to an infection, even though receiving a proper dose of penicillin. Patients with infection must still stimulate those defense mechanisms, such as antibody or leukocytes or plasma cells or specific globulin, that are required for final eradication of a pathogen from a lesion.

No amount of penicillin will result in bacterial cure of a patient's infection when he cannot respond with effective defenses—specific and nonspecific. Penicillin is an effective bacterial antagonist against many species and strains of microbes causing human disease; it is not a therapeutic panacea and can be used only as an adjunct to total care of a patient infected.

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THE TETRACYCLINES

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The pharmacology of the tetracycline antibiotics was reviewed by Shwachman and Schuster[36] in 1956. Since then more detailed pharmacologic studies have been conducted, and a series of additives purported to increase gastrointestinal absorption, new intramuscular preparations, combinations with other antibiotics—including antifungal agents—and an additional homologue, demethylchlortetracycline, have been introduced for clinical use. Despite these advances, the practicing physician's therapeutic armamentarium has not been significantly increased because the antimicrobial range of these drugs has not been extended, and there remains virtual cross resistance among all the available homologues.

SOURCE

The initial tetracycline, chlortetracycline (CTC), was isolated from *Streptomyces aureofaciens* by Duggar[9] in 1948, followed by oxytetracycline (OTC) in 1950, produced by *Streptomyces rimosus*,[15] and tetracycline (TC) in 1952.[3] Tetracycline was originally prepared by catalytic hydrogenation of the chlorine radical of CTC. Demethylchlortetracycline (DMCT), produced by a mutant of Duggar's original strain, was described in 1957[30] and introduced for clinical use in 1959.

Many other homologues have been produced. These include a series of halogen-substituted compounds,[7] various demethyl derivatives,[30] and other modifications of the basic tetracycline molecule.[33] Some of these are presently under clinical investigation, but none as yet are available for therapeutic use.

PHYSICAL AND CHEMICAL PROPERTIES

The structural formulas of the 4 tetracycline homologues currently in

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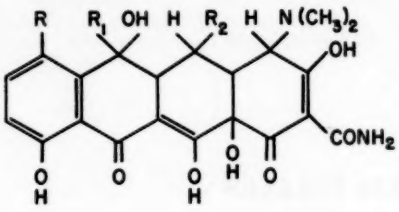
use are presented in Figure 6. The pyrrolidinomethyl derivative of tetra-



	R^a	R_1^a	R_2^a
TETRACYCLINE	H	CH_3	H
CHLORTETRACYCLINE	CL	CH_3	H
OXYTETRACYCLINE	H	CH_3	OH
DEMETHYLCHLORTETRACYCLINE	CL	H	H

Fig. 6. Structural formulas of the tetracyclines.

cycline is formed by substitution at the $-CONH_2$ position.[34] This derivative is much more soluble in aqueous solutions than tetracycline. Its principal use is in intramuscular preparations, but like the hydrochlorides of all the tetracycline homologues, it is administered together with a local anesthetic to minimize the pain following injection.[6, 39]

As a group the tetracycline antibiotics are amphoteric crystalline compounds soluble in glycol ethers, pyridine and dilute acid and alkali, very slightly soluble in water and in lower molecular weight alcohols, and insoluble in ether and hydrocarbons. The acid salts (used therapeutically) are well formed crystalline compounds with high solubilities in water.[33]

METHOD OF ASSAY

A detailed account of the standard assay procedures for the commonly used antibiotics may be found in the excellent laboratory manual prepared by Grove and Randall[16] of the Division of Antibiotics of the federal Food and Drug Administration. Assay methods for the tetracyclines may be classified into microbiologic and chemical. Of the microbiologic methods, the cylinder-plate assay utilizing *Bacillus cereus, var. mycoides,* as the test organism is most commonly used for accurate measurement of microbially active drug in biologic fluids. Serum concentrations are determined by diluting both the unknown and the simultaneous run standard solutions in human serum or solutions of bovine albumin. Results obtained by this method give total antibiotic concentration, and do not report bound versus free drug. A turbidimetric method utilizing a strain of *Staphylococcus aureus* is also available and is particularly useful in measuring concentrations of drug in urine. Chemical methods are generally reserved for assay of production

lots and pharmaceutical dosage forms and studies of mixtures. These include a ferric chloride colorimetric, an acid colorimetric, ultraviolet spectrophotometric and fluorometric determinations. The last-mentioned method has also been adapted for determination of drug in biologic fluids. Concentration of drug is reported in micrograms per milliliter or gram.

The foregoing methods are of great value in obtaining accurate assays for the performance of pharmacologic studies of the individual homologues. They are of considerably less value, and may at times be subject to erroneous interpretation, when used to compare the antimicrobial *activity* achieved in biologic fluids by the various homologues. This is because the homologues differ in activity by weight against different microorganisms, and this frequently differs between strains of the same species.[14, 17] For this reason investigators interested in comparing homologues generally use a twofold broth dilution method of assay utilizing as the test organisms commonly encountered bacteria isolated from patients. All such studies must include a statement of the minimum inhibiting concentration of each homologue under study for the assay organism to be used. In comparative studies, specimens representing each of the homologues should be assayed on the same day because of the inherent variability of the twofold dilution method. Despite somewhat less accuracy than the cylinder plate method, and the failure of the dilution method to take protein binding fully into account, it has been found to be a reliable method for clinical studies.[22]

ANTIMICROBIAL SPECTRUM

The tetracycline antibiotics inhibit a broad range of microbial agents, including both gram-positive and gram-negative bacteria, *M. tuberculosis*, rickettsiae, the psitticosis-lymphogranuloma venereum group of large viruses, and the agent of primary atypical pneumonia (Eaton agent). The most sensitive, clinically important organisms in the gram-positive group include the pneumococcus, group A beta hemolytic streptococci, *Str. viridans* and, depending on the extent of utilization in a particular area, the staphylococcus. Among the gram-negative group sensitive organisms include most *Escherichia coli*, the meningococcus, gonococcus, *Hemophilus influenzae*, pasteurella, brucella and shigella strains. Aerobacter and proteus species vary considerably in sensitivity to the tetracyclines. Only a few strains of *Ps. aeruginosa* have been found to be sensitive.[14, 17]

MODE OF ACTION

The precise mechanism by which the tetracyclines exert their antimicrobial action is unknown. An excellent review of the literature up

to 1956 was prepared by Eagle and Saz.[10] The following effects appear to have been established. The tetracyclines are active chelating compounds (*vide infra*) forming firm unions with divalent and trivalent cations, and may thereby interfere with enzymes requiring such cations as cofactors. They appear to interfere with the phosphorylation of glucose in both bacterial and mammalian cells. Their action is in part reversed by some vitamins and amino acids, particularly riboflavin, and they cause a derangement of cellular mechanisms leading to protein and nucleic acid synthesis.

ANTIMICROBIAL RESISTANCE

One of the great difficulties encountered in the use of the tetracycline antibiotics had been the emergence of resistant bacteria. The over-all problem was summarized by Finland[12] in 1955, and has not changed much since that time. The problem separates itself into two distinct parts: the development of resistant strains during the course of therapy by means of mutation and selection, and the superimposition of strains of established resistance after suppression of the susceptible microflora. It is frequently difficult to distinguish between these two possibilities in clinical settings. The studies of Knight et al.[21] on the appearance of antibiotic-resistant staphylococci in patients treated with tetracycline following admission to a medical service favor the concept of superimposition of antibiotic-resistant strains by continued exposure of patients and personnel to the drug. These authors found that within 4 to 5 days after institution of tetracycline therapy their population converted from about 18 to 90 per cent harboring tetracycline-resistant strains. A similar effect has been demonstrated with other antibiotics given prophylactically, erythromycin in particular.[26] Gram-negative organisms multiplying in complicated urinary tract infections, particularly in the presence of an indwelling catheter, tend to develop resistance to tetracycline rapidly, generally by replacement of sensitive species by naturally occurring resistant ones. Resistant strains of *Str. viridans* have been encountered during the course of treatment of subacute bacterial endocarditis with chlortetracycline. In contrast, group A beta hemolytic streptococci and pneumococci have remained sensitive to the tetracyclines, and only minor changes have been encountered with *N. gonorrhoeae* and *N. meningitidis*.[14, 17]

BACTERIOSTATIC VERSUS BACTERICIDAL ACTIVITY

In considering whether a drug is behaving as a bacteriostatic (suppressing multiplication) or as a bactericidal (sterilizing) agent, one must clearly distinguish between results obtained in tests in vitro and in vivo. Minimum inhibiting concentrations reported in the literature

usually are based on bacteriostatic end-points; considerably more drug may be necessary to sterilize the test organism. In addition, since these end-points will vary, depending upon the pH and chemical constituents of the medium and upon inoculum size and the presence of serum, it is not always easy to predict what will occur in the treatment of specific infections in laboratory animals and in man.

Although the tetracyclines are generally considered to be bacteriostatic agents, they may at times *appear* to exert a bactericidal effect in certain clinical situations. For example, they have been found to be as effective as penicillin in treatment of uncomplicated pneumococcal pneumonia, presumably owing to aid rendered by active host defense mechanisms.[27] Although of considerable value, they are less effective than penicillin in eradicating streptococci from the oropharynx and in inhibiting subsequent formation of antistreptolysin O.[19] In addition, the relation between time of initiation of therapy to onset of a disease may be of considerable importance, and this may be related to the bacteriostatic effect of these drugs. Thus Overholt et al.[31] found that in treating patients with laboratory-acquired tularemia, relapses frequently occurred when treatment was begun during the initial week of illness; relapses were fewer when treatment was begun approximately one week after onset, presumably after host defense mechanisms had begun to come into action. This phenomenon was not encountered when streptomycin, a bactericidal agent, was used.

ABSORPTION

The tetracyclines are incompletely absorbed from the gastrointestinal tract. Large amounts can be recovered in the stools after oral administration. Incomplete absorption may be responsible for the profound changes in the fecal flora noted concurrent with their use. Shortly after the introduction of CTC, aluminum hydroxide gel was found to interfere with absorption, but most workers reported that food, milk and carboxymethylcellulose lacked this effect, and these substances were actually recommended to reduce gastric irritation resulting from oral doses. More detailed studies in experimental animals and man have demonstrated a depressing effect of divalent and trivalent cations on blood levels achieved with oral doses.[5, 37] It is now recommended that, to obtain optimal absorption, the tetracyclines be administered during the fasting state.

The subject of the formation of inactive chelates with metallic cations by the tetracyclines has been thoroughly reviewed by Weinberg.[38] Manufacturers have attempted to devise means to counter the effect. Of the many excipients tried, four have been studied in human beings and introduced into therapy: citric acid, a phosphate complex, sodium hexametaphosphate, and glucosamine hydrochloride.

A critical analysis of their role in antibiotic blood level enhancement has been presented by Finland.[13] In brief, many of the studies purporting to demonstrate an enhancing effect upon TC absorption were hampered by one or more of the following: (1) the filler in the capsules used contained dicalcium phosphate, and some also contained small amounts of magnesium salts; (2) the actual content of the antibiotic at the time of the study was not stated; (3) data favorable to one or another preparation were inappropriately emphasized; (4) data obtained from other sources, some uncontrolled and others carefully controlled with cross-over studies, were uncritically combined and analyzed; and (5) small, clinically unimportant differences in antibiotic concentration in the blood were given undue emphasis. In other studies in man in which these defects were largely eliminated, the effects of various excipients, although in some cases statistically significant, were so small as to warrant the conclusion that for therapeutic purposes their addition was of no great importance.[2, 23]

The most detailed study of the site of absorption of TC was performed by Pindell and associates[32] in dogs. They prepared a series of isolated segments of the gastrointestinal tract, leaving the blood supply intact. Absorption of TC was determined by serial measurement of the concentration in the blood after instillation into the different segments. The drug was most rapidly absorped from the duodenum and ileum; peak levels in the blood were reached within a half hour, and were about as high from the duodenum as from the ileum. Absorption from the stomach was delayed so that the peak was more sustained than from the other sites. Relatively little drug was absorbed from the colon, in agreement with earlier studies in man.[18] The observations of Pindell et al. are supported, in part, by those of Danopoulis et al.,[4] who noted that a half hour after oral ingestion of OTC in dogs, blood levels were much higher in the left gastric than in the superior mesenteric vein, indicating gastric absorption at that time, but the latter authors did not study absorption beyond this brief period.

DISTRIBUTION

The tetracyclines appear in the milk of lactating patients, pass the placenta into the fetus, and appear in the saliva, cornea, sclera, iris and vitreous humor. The concentrations of all the homologues are lower in the cerebrospinal fluid than in the blood. Wood and Kipnis[40] found that penetration into the cerebrospinal fluid was best obtained with TC, the poorest with CTC, while OTC was intermediate. CTC appears in the bile at a concentration 8 to 16 times that observed in the serum; DMCT is also concentrated in the liver and excreted in the bile, with bile-serum ratios of 2:32. Similar high biliary concentrations have been noted with the other homologues.

Detailed studies of tissue distribution in experimental animals and man have also been conducted using sensitive fluorometric and radioisotope labeling methods. The drugs appear to be sequestered by fast-growing tissues, liver, tumors, and areas of new bone formation. DuBuy and Showacre[8] have recently found that tetracycline fluorophores are concentrated in the mitochondria of both mammalian and bacterial cells. Small amounts of tetracycline remain tightly bound by chelation to bone calcium long after disappearance from all other organs.

BINDING TO PLASMA PROTEINS

The fraction of active drug bound to plasma proteins differs among the various homologues.[24, 42] As shown in Table 8, CTC and DMTC are

TABLE 8. *Distribution and Excretion of 4 Tetracycline Homologues after Intravenous Injection of 500 Mg. of Each in 4 Normal Young Men*[24]

RATES	TC	OTC	CTC	DMCT
Half-life in serum (hours)	8.5	9.2	5.6	12.7
Renal clearance (ml./min./1.73 m.²)	74	99	32	35
% of dose excreted in 96 hours	60	70	18	39
% serum protein binding	31	20	48	51

most highly bound, followed by TC and OTC. This binding appears to be reversible, and is in all likelihood responsible for differences noted in the rate of renal clearance.

EXCRETION AND FATE

The principal mechanism of excretion is by the kidneys, probably by means of simple glomerular filtration. The rate of excretion is not altered by rate of urine flow, nor by the urine pH. The excretion rates, as determined in man, are listed in Table 8.[24] OTC is most rapidly and completely excreted, followed by TC, DMTC and CTC. The over-all nonrenal excretion rate (nonrenal clearance) is similar for all the homologues except CTC. This homologue is rapidly converted to an inactive product on exposure to alkaline solutions at body temperature. It is of some interest that despite stability of DMCT in vitro, it is rendered inactive or eliminated from the body at the same rate, as determined by nonrenal clearance rates in man, as the remaining homologues.[24] The prolonged blood levels achieved with DMCT are due to its relatively slow renal clearance and stability in vivo greater than CTC.

TC and OTC (and undoubtedly DMCT as well) tend to accumulate in the blood of patients with renal failure when given continuously. Wood and co-authors[41] observed a serum concentration of 80 mg. of TC per milliliter in an oliguric patient on the fourth day of therapy. The half-life of single doses of TC and CTC, as shown in Table 9,

TABLE 9. *Effect of Acute Renal Failure on Persistence of Tetracycline and Chlortetracycline in Blood*[25]

	HALF-LIFE IN SERUM (HOURS)			
TC			CTC	
Oliguric patients	1	108	Oliguric patients	1 6.9
	2	> 2½ days		2 11.0
	3	57		3 6.8
	4	101		4 8.4
	5	108		5 10.1
Normal patients		8.5		6 8.9
			Normal patients	5.6

differs in oliguric patients (less than 400 ml. of urine excreted per day). The half-life of microbially active tetracycline increases from values in normal persons of about 8 hours up to 108 hours in patients with renal shutdown, while that of CTC increases from about 6 hours to only 7 to 11 hours.[25] These profound differences between homologues differing only in the presence or absence of a chlorine atom are due to the lability in vivo of CTC referred to above. Thus, in treatment of uremic patients, TC used sparingly will produce therapeutic blood levels which can be attained with CTC given only in usual doses.

TOXICITY AND UNTOWARD EFFECTS

The most frequent and distressing complications of tetracycline therapy have been nausea, vomiting and diarrhea, the last at times severe when accompanied by overgrowth of resistant strains of *S. aureus* in the feces. In general, these side effects have been infrequent and mild when minimum effective doses (1 gm. daily of TC, CTC and OTC, or 600 mg. of DMCT) in divided doses in adults were used, and their liability to produce diarrhea has been slight with moderate doses. The severe diarrheas, including staphylococcal enteritis, usually subside promptly if recognized early, and if the drug is discontinued and proper hydration along with antidiarrheal therapy is instituted. These complications are generally absent when moderate doses are given intravenously.

Although the gastrointestinal complications of therapy with the tetracyclines are the most frequent and so have received the most attention, certain other more subtle complications are of interest. Each of the three earlier homologues has been shown to produce, during prolonged therapy, morphologic and functional changes in the liver, a negative nitrogen balance and increased riboflavin excretion into the urine. Elevation of the nonprotein nitrogen level in the blood during OTC therapy has also been reported in man.[1] Rabbits given large doses of tetracyclines exhibit rising nonprotein nitrogen in the blood, anorexia, weight loss, lethargy, convulsions and respiratory failure.[11]

Another indirect effect of tetracycline therapy, peptic ulceration and bleeding in uremic patients, has been reported by Lieber and Desneaux.[28] This effect was studied in detail by Lieber and Lefevre,[29] who found the low level of free and total acid in the gastric juice of uremic patients to be associated with high gastric ammonia content; when OTC (or other antibiotics) was administered, the gastric ammonia was stoichiometrically replaced by urea, presumably owing to suppression of formation of bacterial urease in the gastric mucosa, resulting in an increase in gastric acid. Thus the protective effect upon the gastric mucosa afforded by ammonia released from high concentrations of urea in the uremic patient was abolished by antibiotic therapy and, in some cases, resulted in hemorrhage and ulceration.

Drug fevers and various rashes have been observed with each of the tetracycline drugs, but have been relatively infrequent. There have been essentially no blood dyscrasias clearly attributable to them. Pruritus ani and vulvae have been encountered with varying frequency in some groups of patients. As with all antibiotics, particularly those with a wide spectrum, superinfections caused by overgrowth of resistant organisms, including staphylococci, enteric bacteria, yeasts and fungi, have been reported with varying frequency. Superinfections are particularly frequent and severe in hospitalized patients treated for long periods or with large doses and in patients with other serious and debilitating diseases, especially those receiving therapy with other toxic agents such as radiation, antitumor drugs and adrenocortical hormones. Strains of Candida, in particular, are frequently increased in the feces during treatment with tetracyclines, and their numbers can be reduced by concomitant administration of nystatin or amphotericin B. The clinical significance of monilia in most cases is questionable. Nutritional deficiencies, some of specific types and allegedly reversible or preventable by administration of the specific vitamins, have also been noted. These also are difficult to assess.

Of particular interest recently has been the occurrence of an exaggerated sunburn reaction resulting from direct exposure of patients to sunlight during therapy with moderate or large doses of DMCT; such reactions have been only rarely noted with the other homologues. A recent review[35] of untoward reactions ascribed to DMCT reports photosensitivity in about 1.1 per cent of recipients, but the exact incidence is unknown.

THERAPEUTIC INDICATIONS

The tetracyclines have a wide antimicrobial spectrum, are readily administered, and are relatively free from hazardous toxic reactions. They have been widely used since CTC was first introduced in 1948. Principal drawbacks are expense (when compared to injectible penicillin

and sulfonamides), general bacteriostatic action (of considerable importance in infections in which the host response is either limited or relatively ineffective, such as subacute bacterial endocarditis, brucellosis, tularemia, typhoid carriers), the superimposition of resistant S. *aureus* or naturally resistant coliforms, particularly when the drugs are used prophylactically, and the propensity of S. *aureus* and coliform organisms to develop resistance during therapy.

They are effective against the organisms generally found in the respiratory and urinary tracts. This group of drugs is particularly favored by many physicians for infections of uncertain etiology. In many instances, however, these infections may be viral, or other drugs such as penicillin may be more effective. Most of the childhood fevers of unknown origin are of viral etiology, and are not responsive to any of the presently available antimicrobial agents. Most uncomplicated infections of the urinary tract respond well to the relatively inexpensive sulfonamides. Tetracyclines and other antibiotics are of only limited value in complicated urinary tract infections.

The tetracyclines are effective in amebiasis, and very useful in rickettsial infections and disease produced by the lymphogranuloma-psitticosis group of viruses; their usefulness in the treatment of primary atypical pneumonia due to the Eaton agent has been recently re-emphasized in the elegant studies of Kingston et al.[20] They are of no value as antifungal agents, and of limited value in tuberculosis.

DMCT shares almost all the advantages and disadvantages of the other homologues. The lower dose form (150 mg. as opposed to 250 mg. per capsule of the others) diminishes the advantages of more prolonged action and greater antimicrobial activity of this homologue; photosensitivity is occasionally troublesome. Its main advantages, as currently compounded, are that the daily regimen may be divided into doses given every 8 to 12 hours rather than the customary 6-hour intervals used for the other tetracyclines, and that there is a tendency for more prolonged antimicrobial activity after cessation of therapy.

CONCLUSION

It would appear from this brief account that the tetracyclines, although of great clinical value, are by no means the drugs of choice for many infections. They are poor substitutes for good bacteriologic evaluation, and are potentially hazardous when used as prophylactic agents. They, like all other antibiotics, are most helpful when the physician, first, considers the probable nature of the disease he is attempting to treat, the most likely organisms to be dealt with, and the most suitable drug for those organisms; and, second, has taken time to obtain smears and cultures before instituting therapy to confirm or deny his initial impression.

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STREPTOMYCIN

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The discovery of streptomycin in 1944 was the result of deliberate and intense search by Waksman and his colleagues for an antibiotic substance similiar to penicillin, which would supplement its lack of activity against gram-negative organisms. A strain of Actinomyces had been isolated by Waksman in 1919 from which a sporulating strain, *Streptomyces griseus*, was separated. The antibiotic streptomycin was obtained from certain strains of this streptomycete when grown in aerated cultures on media which contained meat extract. The discovery that this new antibiotic was active against acid-fast organisms provided an important stimulus to the initial development. It is of some interest to note that this actinomycete, Streptomyces, includes strains which yield chloramphenicol, chlortetracycline (Aureomycin), oxytetracycline (Terramycin), erythromycin and neomycin.

CHEMISTRY

A great deal of information has accumulated about the chemical structure and behavior of streptomycin—a carbohydrate derivative, N-methyl-L-glucosaminido-streptosido-streptidine. The chemical structure is composed of two main segments, streptidine and disaccharide streptobiosamine, linked by a glucoside. Streptomycin acts as an organic base which forms salts with acids; the hydrochloride and the sulfate are used clinically. Dihydrostreptomycin is produced by catalytic reduction of streptomycin by hydrogen. Streptomycin reacts with alkaline copper solutions and, in a concentration of 1000 micrograms or more in the urine, reduces Benedict's solution.[10]

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Streptomycin was quantitated initially in units which were determined on the basis of bioassay, but, at present, amounts of the drug are expressed in terms of the weight of the pure base in micrograms, and commercial preparations of the sulfate are expressed in terms of weight of the pure base. The antibiotic is stable and shows no loss of potency when stored at room temperature for a year in the dry state or in solution for a period of 60 days at room temperature.

ANTIMICROBIAL ACTION

Streptomycin is bacteriostatic for susceptible organisms in low concentration and is bactericidal at the usually attainable levels. The mechanism of action, similar to that of other antibiotics, is probably through interference and reaction with basic cell chemical reactions. Most of the reported evidence on streptomycin suggests an interference with oxidation-reduction reactions in bacterial cells. A number of factors which have been shown to influence the action of streptomycin in vitro may have implications in its clinical use. Streptomycin is more active in alkaline than in acid solution, for which reason alkali is sometimes administered during streptomycin therapy of urinary tract infections.[3] Streptomycin activity in vitro is decreased with increasing size of the inoculum. The fact that pus is usually acid in reaction, together with decreased activity with increased inoculum size, may explain the failures of streptomycin therapy in cases with walled-off collections of pus.

Among other factors which have been observed to change the action in vitro of this drug are the addition of a wide variety of salts—not including those in normal urine—the introduction of glucose, and the introduction of a variety of organic substances and oxidizing and reducing agents. Blood, serum and spinal fluid have been shown to decrease the antibacterial effect of the drug, but probably as a result of the increase of bacterial growth by these substances.

BACTERIAL RESISTANCE TO STREPTOMYCIN

Soon after the discovery of this antibiotic it was shown that organisms could develop increased resistance, especially when grown in media which contain increasing amounts of the antibiotic. This increased resistance is not due to the production by the organisms of a streptomycin-inhibiting substance analogous to penicillinase. The "stepwise" development of resistance common to both penicillin and streptomycin is significantly different. This has led to the terminology of "penicillin pattern of resistance" and "streptomycin pattern of resistance."

In a bacterial population there nearly always exist a few organisms which, because of their ability to produce penicillinase, are penicillin-resistant. With exposure to penicillin through several generations, these penicillinase-producers successively slowly emerge as the predominant strain, so that eventually the bacterial population is almost completely penicillin-resistant. A significant number of resistant organisms must be present at the first step in order for this slowly progressive resistance to proceed to general resistance.

Streptomycin, on the other hand, shows a different pattern for the development of resistance. This is due to great variation in the resistance of the first-step mutants, which may vary from those only slightly more resistant than the original strain to organisms completely resistant to streptomycin. Thus stepwise development of resistance occurs with streptomycin at a greatly increased rate and to a recognized high extent. Individual components which comprise a single strain of bacteria can thus vary widely in resistance to the antibiotic and form a typical standard curve of distribution, if it were possible to determine the sensitivity of each organism. The rapid elimination of sensitive members of a given population of organisms allows a small number of resistant mutants, through their rapid reproduction, to comprise the total population in a very few "steps."

The biochemical mechanisms involved in the development of resistance to an antibiotic by a bacterial organism vary among different bacterial strains and, more importantly, with respect to different antibiotics. Resistance to streptomycin is not the result of the production by the organism of a streptomycinase analogous to the penicillinase produced by penicillin-resistant bacteria. Streptomycin resistance in sensitive strains was induced by Alexander and Leidy[1] by exposing sensitive strains of extracts to resistant strains, and a transfer of deoxyribonucleic acid from the resistant to the sensitive strain was demonstrated. A number of other observations confirm the conclusions that the mechanism of streptomycin resistance is found in the biochemistry of the cell and the cell nucleus, in contrast to the mechanism in the case of penicillin resistance, which depends upon extracellular penicillinase production by which bacteria are able to convert penicillin to penicillic acid.

In addition to this phenomenon of resistance to the antibiotic, Miller[9] has described a variant of meningococcus which apparently requires streptomycin for growth. Certain other organisms have since been reported to be dependent upon streptomycin for their growth after exposure in vitro to high concentrations of the drug. Studies of these organisms indicate that, although in the usual case of antibiotic activity the drug interferes with some metabolic process, strains can be found which are apparently dependent upon the antibiotic for their

metabolic activity. It seems that dependence upon the antibiotic is a phenomenon which is unlike the more commonly observed alteration of resistant strains.

Experiments in vivo have shown that certain strains of these streptomycin-dependent organisms can be injected into animals with only low resultant mortality. When streptomycin is given concomitantly, the mortality increases. The clinical applications of this phenomenon are not known; it is possible that search for such dependent strains, utilizing special techniques, might reveal some examples.

Cross resistance between streptomycin and other antibiotics is not common; Haight, Wilcox and Finland[2] reported cross resistance between it and neomycin.

SYNERGISM AND ANTAGONISM

The term "synergism" as applied to antimicrobial activity indicates the ability of two drugs to increase the rate of rapid bactericidal action or the rate of cure of experimental or clinical infections beyond that obtainable by simple additive effects of the agents. Jawetz[7] identifies streptomycin as one of the antimicrobial agents which act most effectively against rapidly multiplying bacteria. These drugs are classified as bactericidal because the bactericidal concentration is only slightly higher than the bacteriostatic level. The combined action of penicillin and streptomycin on enterococci is well known and is the most dramatic clinical example of this synergistic phenomenon. Shaffer and Spink[12] demonstrated a synergistic action between streptomycin and sulfadiazine against Brucella in vivo, and clinical experience has confirmed these experimental findings.[13] Further evidence has accumulated that streptomycin in combination with tetracycline or chloramphenicol is more effective in vivo than either of the drugs singly. The combined action of streptomycin and isoniazid[6] is now well known. The early experiments in vivo which demonstrated a synergistic relation between these two drugs has been confirmed by observations in the treatment of clinical forms of tuberculosis.

The extensive investigations of Jawetz[7] and his associates demonstrated that the tetracyclines and chloramphenicol may interfere with the antimicrobial activity in vitro both of streptomycin and penicillin, but state that antagonism between antimicrobial agents is most uncommon in clinical practice.

DISTRIBUTION AND ABSORPTION

Intramuscular injection of streptomycin results in wide distribution through most tissues of the body. Concentrations are higher in the

kidney than in most other organs and lowest in the pus of abscesses. Significant amounts of streptomycin do not appear in the cerebrospinal fluid in the absence of meningeal inflammatory reaction, but in patients with meningitis therapeutic levels are attained readily at approximately half of the blood concentration of the drug. Levels in the peritoneal fluid are high, and in patients with peritonitis they may equal those in the blood.

Streptomycin is poorly absorbed from the gastrointestinal tract, and significant blood levels are not found after the inhalation of streptomycin aerosol preparations. Excretion of streptomycin is principally through the kidneys. This is rapid for the first 4 hours after an intramuscular administration, and by the end of 12 hours most of the drug has been excreted in the urine, but at a rate slower than that of penicillin. In cases of renal insufficiency continued administration of streptomycin results in blood concentration which may rise to toxic levels. In such cases very careful observations must be made of blood levels of the drug as a guide in determining the dosage.

TOXICITY

Untoward reactions to streptomycin (and dihydrostreptomycin) may be considered under two categories: neurotoxic and allergic reactions.

Damage to the eighth cranial nerve during long-term use of streptomycin was first described in 1945 by Hinshaw and Feldman.[5] The most common form of neurotoxicity from streptomycin is damage to the vestibular apparatus, the incidence of which is directly proportional to the duration of therapy, the total amount of streptomycin administered and the age of the patient. In conventional dosage given for less than seven days, the incidence of such toxic reactions is extremely rare. Patients who exhibit labyrinthine damage may go through an acute phase in which nausea, vomiting and vertigo occur in the upright position. This is followed by a period in which the patient adapts to the impairment through the use of visual effort and proprioceptive function. Full recovery is common, especially in the pediatric age group, and no specific treatment is necessary.

Auditory damage is another neurotoxic effect of streptomycin. Deafness is extremely rare, but some decrease in auditory acuity has been shown to occur in a significant number of patients who have received this drug for more than one week. This decrease in hearing is sometimes manifested by a prodromal period of tinnitus, during which time the antibiotic may be discontinued with no resultant impairment in hearing. It appears that the incidence of auditory impairment is related more to the total daily dose and route of administration than to the duration of therapy. Lincoln, Sordillo and Davies[8] state that

survivors (of long-term therapy) who received no intrathecal therapy with streptomycin had no perceptive loss of hearing. Careful judgment in long-term therapy can obviate this untoward phenomenon.

With the introduction of dihydrostreptomycin in 1946, evidence demonstrated that it was equally active as streptomycin against certain bacteria as well as tubercle bacilli. It was then proposed that equal parts of streptomycin and dihydrostreptomycin would decrease the toxic effects peculiar to either drug because of the reduction in the total amount of each which was administered. The evidence that toxic manifestations of dihydrostreptomycin appeared later than those due to streptomycin seemed to be an added advantage. It was soon apparent, however, that potential toxicity due to dihydrostreptomycin was more serious than that due to streptomycin, that dihydrostreptomycin produced far more severe damage to auditory function, and that complete deafness was far more frequent.

The conclusions reached during these initial years of experience with dihydrostreptomycin were that it was equal in effectiveness to streptomycin, but at least equally toxic—streptomycin caused more damage to the vestibular apparatus, and dihydrostreptomycin caused more auditory damage. In 1954 Harrison[4] called attention to permanent deafness that could occur after administration of only small doses of dihydrostreptomycin which followed a latent period (from several weeks up to six months from the administration of the drug to the onset of the hearing loss). This latent period is unique for dihydrostreptomycin and is particularly important for the practicing physician to note. All other drugs which produce auditory damage do so immediately, during or shortly after the period of administration. The previously extensive use of preparations which combined streptomycin and dihydrostreptomycin for minor infections or as "prophylaxis" may have been responsible for deafness which was attributed to streptomycin, but was, in fact, actually due to the associated use of dihydrostreptomycin. Sheehy,[14] in reporting 26 cases of hearing loss due to ototoxic antibiotics, records 20 as due to dihydrostreptomycin, 4 to neomycin and 2 to kanamycin, but includes none due to streptomycin. Dihydrostreptomycin should not be used for short-term therapy; only rarely in long-term therapy does it offer the advantage originally assumed, especially because present knowledge of adequate antituberculosis therapy affords reduction in toxicity due to streptomycin.

A number of allergic reactions to streptomycin have been reported which include skin rash following parenteral administration or skin contact, drug fever, angioneurotic edema and asthma. Eosinophilia is found in the majority of patients who receive streptomycin for more than 7 days and, on rare occasions, may reach levels as high as 70 per

cent. Blood dyscrasias are extremely rare, but have been reported and include pancytopenia, anemia, thrombocytopenia and moderate leukopenia. Contact dermatitis in patients, as well as among doctors and nurses who administer the drug, may be erythematous, maculopapular, urticarial or hemorrhagic and may recur after several months without exposure. Cross sensitivity between streptomycin and neomycin as manifested by skin reactions has been reported. Neomycin, which is obtained from *Streptomyces fradiae*, demonstrates a possible sensitization relation between various strains of this fungus.

As with penicillin and tetracycline, therapy with streptomycin may cause suppression of the normal flora of the mouth and intestinal tract and permit organisms which are not sensitive to this antibiotic to become predominant and produce disease. Streptomycin is not effective against many gram-positive cocci, and *Staphylococcus aureus* may become predominant in cultures during the second and third weeks after initiation of therapy with it.

CLINICAL APPLICATION

The especial value of streptomycin in the treatment of infections depends upon its bactericidal action on those organisms against which it is effective. Few other antibiotics or therapeutic agents have equal power to kill sensitive bacteria as rapidly.

Unfortunately, even those bacteria which are susceptible to streptomycin will frequently develop resistance to it, so that in some instances rapid lethal activity may be effective for only a few days. For this reason its use in therapy is often combined with bacteriostatic agents: tetracycline, chloramphenicol, sulfonamides, and others, which slow up the rate of reproduction of the organism, reduce the emergence of insusceptible mutants, and thus prolong the bactericidal action of streptomycin.

There are definite limitations to the use of this antibiotic. It is the single antibiotic of choice in only a few instances, although this use is extended by its combination with other drugs. In almost every clinical situation in which streptomycin is valuable for its bactericidal properties, the concomitant use of bacteriostatic agents prolongs its usefulness and improves the therapeutic effect. In some situations it may be given empirically, but, as with any antibiotic, specific sensitivity of the pathogen should be determined if possible. This determination of specificity should be carried out especially in the use of streptomycin in combination with other drugs; refined methods of sensitivity testing may thus determine the best combination for the desired effect.

Certain antagonistic actions of streptomycin, when combined in

vitro with other antibiotics, have been previously noted in experiments, but these antagonisms are not of serious import in the dosage and duration used clinically.

Streptomycin is not absorbed from the gut and is used infrequently and without great efficacy for eradication of bacteria within the intestine. Other agents are more appropriate for this purpose.

Streptomycin should not be given intravenously, although warnings of its nephrotoxicity when given by this route are not adequately emphasized. When given intramuscularly, it is absorbed so promptly and efficiently as to make intravenous use unnecessary.

The drug penetrates the subarachnoid poorly, although better, fortunately, in the presence of infection of the meninges. It may be given intrathecally, although this is seldom appropriate or necessary in the treatment of meningitis. There are those who sedulously avoid giving any antibiotic intrathecally, and there is little reason in this case for them to abandon their misgivings.[8]

Warnings, both loud and clear, have been sounded of the dangers of streptomycin therapy as well as counsel that it should be given only when the necessity for its use is well considered. These warnings have applied especially to its use in premature infants and have emphasized the advisability of greatly reduced dosage schedules in prematures, newborns, or in patients who have reduced viability. Ross[11] states that usage should be restricted to tuberculosis:

> In our opinion it would not be too far afield to state that with the exception of tuberculosis, the bona fide indications for the use of streptomycin in infants and children have been substantially curtailed in recent years, and the drug may become of historic importance only.

In spite of its recognized toxic effects, this drug has been used widely, alone or in combination, for routine "prophylaxis" in the newborn and premature, for postsurgical cases—even those without known infections. Sinister results can hardly have occurred with great frequency, for they have not occasioned widespread concern.

Probably, as amply documented not only for streptomycin, but also for sulfonamides, chloramphenicol, polymyxin, and others, no potent antibacterial drug should ever be given except in proper dosage, under adequate supervision, and for considerations which are well established—on clinical or laboratory evidence—that it is the drug of choice under the given circumstances and that its therapeutic value outweighs the risks of its administration.

The dosage of streptomycin should be determined specifically, and it should never be given simply as a part of an arbitrarily designed combination, as with penicillin-streptomycin packaged mixtures. It is now well established that dihydrostreptomycin should never be used, singly or in combination, except for the extraordinary and almost

unbelievable circumstances in which a patient who requires the therapeutic use of streptomycin is hypersensitive to it, but is not equally sensitive to dihydrostreptomycin.

DOSAGE

Intramuscular administration is the route of choice. Blood levels are achieved rapidly and persist for six to eight hours.[16] Pain from injection is minimal, and local reaction to the antibiotic is not a common problem except in long-term administration in the therapy of tuberculosis.[11]

The *usual dose* is 20 to 40 mg. per kilogram per day administered intramuscularly in 2 or 3 doses. For the premature, newborn infant and oliguric patient, the dose is 10 mg. per kilogram per day in 2 or 3 divided doses.

Caution: Mixtures should be carefully reviewed before their use to determine their content of streptomycin; dosage should be based on the foregoing recommendations. The rare indications for the use of dihydrostreptomycin should be re-emphasized. Mixtures of antibiotics should exclude those which contain dihydrostreptomycin.

Intrathecal dose is 1.0 mg. per kilogram or less than 20 mg. per day as a solution in a concentration of 5 mg. per milliliter.

Aerosol therapy utilizes 300 mg. 2 to 4 times a day administered as a solution in a concentration of 150 mg. per milliliter using 2 ml. in the aerosol apparatus. Solution for local, intrapleural, intra-articular, intraperitoneal use or for eye and skin application is 50 mg. per milliliter.

Caution: Streptomycin should never be administered intravenously.

SPECIFIC ANTIBACTERIAL THERAPY

Tuberculosis

Streptomycin was one of the first drugs to be used effectively against the tubercle bacillus, and its use recorded some of the first cures of tuberculous meningitis. The introduction of isoniazid (INH) greatly decreased the use of streptomycin for this purpose and, in combination with para-aminosalicyclic acid (PAS), has, to a degree, supplanted its use in tuberculosis. Streptomycin is not used in primary tuberculosis. In every case in which streptomycin is used, it should be combined either with INH or PAS in order to slow bacterial reproduction and impede the rapid emergence of resistant organisms.

Streptomycin is useful in situations of urgent treatment of tuberculous meningitis, miliary tuberculosis, renal or bone and joint involvement, pleurisy, and situations in which rapid therapeutic effect is most to be desired.

The recommended dosage of streptomycin in fulminant tuberculosis is variable. The Committee on Control of Infectious Diseases of the Academy of Pediatrics recommends a daily dose in tuberculous meningitis of 40 to 80 mg. per kilogram per day to a maximum of 1 gm. daily, divided in 2 daily doses (adult maximum dosage: 3.0 gm. daily), and continued for 6 months to 1 year. Other authorities recommend a daily dosage of 20 to 40 mg. per kilogram daily (usually divided into 2 doses) and restrict the period of streptomycin therapy to 6 or 8 weeks, with coincidental use of PAS and INH to be continued for at least 1 year.

With the recognition of the great value of INH in the treatment of tuberculosis, even in the more severe forms of the disease, the importance of coincidental use of streptomycin has diminished, and probably the conventional dosage of 20 mg. per kilogram per day for 6 to 8 weeks is effective in most situations. (See also page 1218.)

Hemophilus Influenzae Meningitis

The treatment of this disease can be accomplished in several ways. Streptomycin, chloramphenicol and sulfonamides are all effective, and cures have been noted with each drug when given singly. Alexander and Leidy[1] report that three or four patients treated with streptomycin failed to respond because of the emergence of resistance of the organism which developed in the course of treatment. Sensitivity tests in *H. influenzae* meningitis require extraordinary skill, however, beyond that of the usual bacteriologic laboratory, so that specific sensitivity to streptomycin is determined with difficulty, and detection of the development of resistance is almost impossible in usual clinical practice. Weinstein[17] states that studies in vitro suggest that the appearance of resistance, and survival and growth of *H. influenzae* do not occur when exposed to streptomycin combined with a sulfonamide. Excellent results have been reported[18] in the treatment of *H. influenzae* meningitis with or without septicemia by the empiric use of streptomycin, 40 mg. per kilogram per day, combined with sulfadiazine, 0.1 to 0.15 gm. per kilogram per day. If streptomycin is continued for only five days, the likelihood of toxic effects is eliminated, and during this short period of therapy emergence of resistant strains is not to be expected. Chloramphenicol may be used together with streptomycin or may be started just as streptomycin is discontinued—in either case along with sulfadiazine or another sulfonamide. All three drugs may thus be used in various combinations, depending on the severity of the infection. The persuasive value of streptomycin in therapy depends upon its prompt bactericidal effect, the other drugs being essentially bacteriostatic in action. The prompt arrest of the disease process may be essential to the prevention of late complications. (See also page 1182.)

Subacute Bacterial Endocarditis

When this disease is due to *Streptococcus viridans*, penicillin is the most essential drug in therapy, but the addition of streptomycin, for at least a part of the period of treatment, often adds to its effectiveness. When enterococci are involved, the organisms are often resistant to penicillin, but penicillin in combination with streptomycin may be far more effective. (See also page 1234.)

Brucellosis

Formerly streptomycin in combination with sulfadiazine, chloramphenicol or a tetracycline was recommended for therapy; more recent recommendations depend upon the prolonged use of tetracycline alone.

Tularemia

Streptomycin in usual dosage is almost universally the drug of choice, although analogy to other infections suggests the appropriateness of adding sulfonamides or tetracyclines to the course of therapy.

Plague

The use of streptomycin in the treatment of *Pasteurella pestis* parallels the use in *Pasteurella tularensis*, although it is recommended that tetracyclines should be given also.

Klebsiella Pneumoniae Infections

The control of infections due to this organism is extremely difficult, but combinations of streptomycin with sulfadiazine, chloramphenicol, tetracycline or polymyxin are recommended.

Escherichia Coli Infections

Streptomycin has variable effectiveness against certain gram-negative rods, including *E. coli* of conventional nature and those strains of high pathogenicity, as well as bacillus proteus and other enteric gram-negative rods. The selection of streptomycin on an empiric basis is questionable, and continued treatment usually involves the determination of specific sensitivity to various drugs and antibiotic agents, alone or in combination.

Streptomycin, alone or in combination with penicillin or other antibiotics, is almost universally given for "prophylaxis" in infancy against infection with enteric gram-negative rods. This use applies to infants

born after rupture of maternal membranes, those born out of asepsis, those with hyaline membrane disease and in other instances in which exposure to enteric organisms is a significant risk. This use is difficult to defend or to evaluate, although it appears to be recommended by those who, in general, refrain from the use of streptomycin. There is some justification for the empiric use of penicillin and streptomycin in infants in whom there is definite soiling of the peritoneum in the course of surgical correction of neonatal abnormalities of the gut. In every instance in which streptomycin is given in infancy, however, the reduced dosage previously noted should be carefully observed.

CONCLUSION

Streptomycin is an extremely valuable agent in some specific bacterial infections in which it has the advantage of extraordinarily rapid bactericidal activity.

It is a potentially toxic agent, although not extremely dangerous under controlled conditions of dosage and duration of administration. It is ordinarily best applied in combination with other chemotherapeutic or antibiotic agents which impede the rapid emergence of insusceptible organisms. Only rarely is it the drug of choice which should be selected empirically.

Streptomycin is used in a number of uncommon infections either as a matter of trial and error or after careful determination of specific sensitivity. As a general rule, it is better to combine streptomycin with another antibiotic under these conditions. This applies, for example, to lepra, listeria, bacterioides, leptospirae, and some other unfamiliar agents in which specific therapy is not well established.

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CHLORAMPHENICOL

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CHEMISTRY

Chloramphenicol is a nitrobenzene compound of small molecular weight containing chlorine in organically bound form. It is a crystalloid with an exceptionally bitter taste, only slightly soluble in water, but readily soluble in propylene glycol and the lower alcohols. It is thermostabile in dry form and in neutral solutions. Antibiotic activity is maintained in strongly acid solution for at least 24 hours, but is rapidly lost in alkaline solutions with a pH above 10. Solutions darken slowly on exposure to light with loss of antibiotic potency.[7]

After isolation in 1947 from culture filtrates of a new soil fungus, *Streptomyces venezuelae*, the chemical formula was soon identified and the antibiotic successfully synthesized (Fig. 7).

The aromatic ring structure appears to be essential for biologic activity. Antibiotic activity is specifically dependent upon the steric configuration of the molecule, since the isomers of chloramphenicol are inactive.[17, 56] A wide variety of alterations in the molecule have been made in an attempt to produce allied drugs with different clinical properties. Most of the changes have resulted in a loss of antibiotic potency, and none have been superior to the parent drug.

MODE OF ACTION

The action of chloramphenicol on susceptible microorganisms is usually bacteriostatic rather than bactericidal. Bacteriostatic effects can be demonstrated at minimal therapeutic concentrations. In some instances with a higher concentration of chloramphenicol, a slow but definite bactericidal effect has been described. More rarely a rapid bactericidal effect has occurred. Sensitivity may vary widely among different bacterial strains within the same species. For example, three strains of *Escherichia coli* have been observed in which the action of chloram-

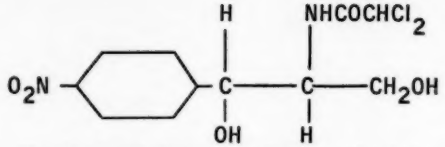

Fig. 7. Chemical structure of chloramphenicol.

phenicol was either predominantly bacteriostatic, slowly bactericidal, or rapidly bactericidal.[56] For practical purposes, the action of chloramphenicol should be considered bacteriostatic unless specific laboratory data demonstrate otherwise.

The principal effect of chloramphenicol on sensitive bacteria is prompt inhibition of protein synthesis.[35, 50, 54, 55] Contributing to this effect are decreased ability to assimilate ammonia and suppression of oxidation.[37, 55] Inhibition occurs, though nucleic acid synthesis, polysaccharide metabolism, phosphorylation or motility are not suppressed even by large doses.[18, 55] One explanation for the depressant effect on protein synthesis emphasizes that the active antibiotic form of chloramphenicol is the D isomer, while most amino acids are L isomers.[17] Interaction occurs between D isomers of one compound and L isomers of another, but not when both compounds are in the D form. Interference with specific enzymatic processes has been demonstrated which differs in various organisms.[57]

The effect of chloramphenicol on the host cells differs from the effect on bacterial cells. Mammalian cells and mitochondria grown in tissue culture, containing therapeutic levels of antibiotic, are protected from inhibition of protein synthesis, but the mechanism by which this occurs is unknown.[57] The enzymatic reduction of chloramphenicol is acomplished by different methods in animal tissues as compared to bacterial organisms,[10] but the significance of these differences in the host is not clear.

One interesting study reported the antibody production by monkeys against the enterobacteria during chloramphenicol treatment.[51] No quantitative or qualitative change in antibody production during infections with *Salmonella typhosa*, *S. typhimurium* and *E. coli* with or without therapy could be shown. Watson proposed that the relapse rate observed during infections with these organisms was related to phagocytosis of the organisms with an increase in the intracellular population rather than to an interference with antibody production.

ANTIMICROBIAL ACTIVITY

Chloramphenicol is effective against a wide variety of pathogenic organisms, including both gram-positive and gram-negative bacteria,

the Rickettsiae, and certain strains of viruses. The sensitivities in vitro of most of the commonly encountered pathogenic microorganisms are presented in Table 10. The concentrations of 5 and 25 micrograms per milliliter were selected because these levels are readily obtained in the body fluids of man with standard clinical doses. As is true with all antibiotics, sensitivity in vitro does not always correlate with results in vivo. Variations in sensitivity from strain to strain within the same species of bacteria have been reported most frequently in gram-negative bacilli.

RESISTANCE

Although occasional changes in bacterial sensitivity to chloramphenicol are reported, they occur infrequently. This is in contrast to the changing sensitivity patterns seen with other antibiotics and has been attributed to restricted use of chloramphenicol. This, however, cannot explain the consistently high incidence of sensitive strains maintained in hospitals where use of the antibiotic has not been curtailed.[2] The suppression of development of resistance must be inherent in the mode of action of the drug.

Fisher[8] has surveyed all publications of experimental and clinical experiences with staphylococci between 1950 and 1958. Although some hospitals have reported an increased incidence of resistant organisms accompanying increased use of the drug,[6, 25] he found an over-all incidence of 9 per cent chloramphenicol-resistant staphylococci with no trend of increased resistance during this period. This agrees with our own experience in which, in a recent survey of staphylococcal infections within the hospital, no resistant strains were found in 258 organisms recovered.

SYNERGISM AND ANTAGONISM

Both synergism and antagonism have been demonstrated when chloramphenicol was combined with other antibiotics in vitro. The clinical significance of these experimental observations has not been evaluated adequately. Hinton and Orr[19] have studied the combined activity of streptomycin and chloramphenicol in experimental infections with *S. typhimurium* and *E. coli* in mice. In bacteriostatic combinations the two drugs were indifferent. But when bactericidal doses of streptomycin were used, an early antagonism occurred, lasting for several hours. The authors report one infant in whom the addition of chloramphenicol to treatment with streptomycin resulted in rapid deterioration and death. Their investigation was started after this experience. Further evaluation needs to be made as to the implications

TABLE 10. *Sensitivity of Pathogenic Microorganisms to Chloramphenicol*

ORGANISMS	NO. OF STRAINS	PER CENT SENSITIVE TO: < 5 μg./ml.	< 25 μg./ml.
Achromobacter species	119	8	38
Actinomyces bovis	3	0	100
Actinomyces israeli	18	100	100
Aerobacter-Klebsiella	968	69	88
Alcaligenes faecalis	24	45	71
Bacillus anitratum	163	4	4
Bacillus anthracis	40	50	100
Bacteroides species	115	62	97
Bartonella bacilliformis	1	100	100
Brucella species	49	92	100
Candida albicans	?	0	0
Clostridia species	51	42	78
Coccidioides immitis	?	0	0
Corynebacterium diphtheriae	185	100	100
Corynebacterium species	400	100	100
Diplococcus pneumoniae	178	99	100
Enterococci	596	61	83
Escherichia coli	1114	68	87
Hemophilus influenzae	203	100	100
Hemophilus parapertussis	12	100	100
Hemophilus pertussis	110	97	100
Leptospira species	6	83	100
Listeria monocytogenes	9	78	100
Malleomyces pseudomallei	6	83	83
Micrococcus pyogenes	5010	49	95
Myobacterium tuberculosis	20	35	100
Neisseria intracellularis	56	89	100
Neisseria gonorrhoeae	172	100	100
Nocardia species	18	0	67
Paracolons	77	33	77
Pasteurella species	18	94	100
Pleuropneumonia-like organisms	32	60	75
Proteus species	867	22	74
Providencia species	25	—	92
Pseudomonas aeruginosa	774	1	10
Pseudomonas species	42	5	60
Salmonella typhosa	120	81	100
Salmonella species	259	74	100
Sarcina species	2	50	100
Shigella species	155	83	100
Streptococci (alpha)	149	96	99
Streptococci (beta)	189	93	98
Streptococci (anaerobic)	5	60	80
Vibrio cholerae	64	84	89

From T. E. Woodward and C. L. Wisseman.[55]

for treatment of severe infections in which an early bactericidal effect is necessary. The development of bacterial resistance to streptomycin was inhibited by the addition of chloramphenicol.

ABSORPTION AND EXCRETION

Crystalline chloramphenicol is absorbed unchanged, and is the metabolically active form of the drug. After oral administration it is rapidly and almost completely absorbed from the gastrointestinal tract.[12, 45] Therapeutic levels appear in the blood within 30 minutes after ingestion, reach their peak in 2 hours and disappear by 12 to 22 hours. The height and duration of the blood levels are proportional to the dose. The circulating chloramphenicol is rapidly conjugated by the liver to a monoglucuronide, which has no biologic activity and is highly water-soluble. A small amount of chloramphenicol is converted, probably also in the liver, to a biologically inactive aminodial hydrolysis product.

Assays for chloramphenicol are carried out by two methods. The microbial assay by means of a turbimetric procedure against *Shigella sonnei* tests for active chloramphenicol only.[21] The chemical assay determines total aromatic nitro compounds, including both active chloramphenicol and the inactive metabolites.[11] When blood specimens are tested by the two methods, the results are in close agreement, demonstrating that most chloramphenicol in the blood is in the active form.[12] Sixty per cent of the active chloramphenicol in the blood stream is carried reversibly bound to the plasma albumin.

Seventy to ninety per cent of an administered dose is recovered in the urine in 24 hours.[12, 13] The rate of excretion is proportional to the blood level. Five to ten per cent of the total urinary excretion is active chloramphenicol. The remainder consists of inactive aromatic nitro compounds, the glucuronide comprising the major portion. The active chloramphenicol is excreted by glomerular filtration. The filtration rates are low, suggesting that the protein-bound portion of chloramphenicol does not pass the glomerular membrane. The glucuronide is excreted by the renal tubules. Clearance of the inactive fraction is three to five times that of creatinine. Of the total dose, 2.7 per cent is excreted in the bile, primarily as chloramphenicol monoglucuronide. Only 1 per cent of the total dose appears in the stool, suggesting that some of the glucuronide is reabsorbed. Bacteria in the intestinal tract can hydrolyze chloramphenicol to aryl amines, which are then reabsorbed and excreted in the urine. Aryl amine levels are negligible in patients with normal metabolism.

Four anuric patients and 11 patients with renal impairment have been studied by Kunin, Glazko and Finland.[27] Serum levels and 24-hour urine excretion after a single intravenous dose of crystalline chlo-

ramphenicol were determined. The serum levels of active chloramphenicol followed the same pattern as in normal persons. The total nitro compounds were elevated and prolonged. Aryl amide levels appeared at 10 hours and persisted for over 120 hours. No toxic effects were noted in these patients from the high and prolonged levels of chloramphenicol metabolites.

Eleven patients with cirrhosis of the liver were tested in the same manner. Three of these showed prolonged serum levels of active chloramphenicol, but urinary excretion in 24 hours was normal, demonstrating a reduced rate of conversion. Poor correlation was seen between levels of active chloramphenicol and indirect bilirubin levels.

DISTRIBUTION

After absorption chloramphenicol rapidly diffuses throughout most of the body fluids. Of the active serum concentration, 30 to 50 per cent is present in the spinal fluid in normal children, slightly higher levels being reported with meningeal irritation.[23, 41, 42, 56] The portion of chloramphenicol bound to plasma proteins is apparently not free to diffuse into the spinal fluid. Limited reports suggest that chloramphenicol penetrates readily into pleural and ascitic fluids, achieving therapeutic concentrations within several hours after oral administration.[56] Chloramphenicol penetrates into both the aqueous and the vitreous humor of the eye after systemic administration. Applied locally, it penetrates into the aqueous humor. Concentration in the saliva parallels blood concentrations, although at lower levels. Chloramphenicol crosses the placental barrier, and concentrations equivalent to 30 to 80 per cent of maternal levels have been found in the infant at birth.[39, 41, 46] No toxic effects have been reported in these infants. Conflicting reports have been presented about the concentration in human milk. One group found the level in the milk to be 50 per cent of the serum level, while the second group failed to detect any antibiotic activity in the milk of 12 women receiving chloramphenicol.[56]

The effectivness of chloramphenicol in some infections caused by intracellular organisms suggests that the antibiotic may penetrate body cells in an active form. Glazko and co-workers[15] reported finding active chloramphenicol bound to the red cells in a higher proportion than could be explained by simple diffusion, and suggested some form of adsorption as an explanation. Chloramphenicol monoglucuronide was present almost entirely in the plasma.

TOXICITY

The toxic reactions to chloramphenicol of main concern are the production of symptoms resembling shock in the premature and the

newborn infant and bone marrow depression occurring in the infant and the older child. The mechanisms of production of these reactions appear to be different, and they will be discussed separately.

Premature and Newborn Infants

Several reports appeared from 1959 to 1961 describing a symptom complex called the gray syndrome in newborns receiving chloramphenicol in doses over 100 mg. per kilogram daily.[1, 28, 30, 49] In most cases the treatment was started within 48 hours after birth, and the majority of the infants affected were premature by birth weight. The symptoms first appeared after three or four days of continued treatment. The first evidence of toxicity was vomiting or regurgitation of feedings followed by refusal to suck, and abdominal distention. Respiratory distress, flaccidity and an ashen gray color followed. Deaths occurred in the seriously affected babies from 24 to 48 hours after the onset of the first symptoms. No characteristic pathologic changes were found at autopsy. There was no correlation between toxic symptoms and appearance of jaundice. Discontinuing chloramphenicol after the appearance of symptoms usually resulted in their disappearance within 24 to 36 hours. Blood levels were reported in a few of these infants and showed progressive accumulation of total nitro compounds to unusually high levels.

In 1949, symptoms resembling the gray syndrome were reported in adult dogs and adult mice given lethal or near-lethal doses of chloramphenicol.[16] In the dogs that died, hydropic degeneration of glomerular capillaries was the only finding at autopsy. After the reports of deaths in newborns two studies were published comparing the toxicity of chloramphenicol in newborn versus adult animals.[24, 31] The gray syndrome appeared in both newborn and adult animals; however, the LD_{50} dose for adults was several times that for newborns on a milligram-per-kilogram basis.

Further studies on newborn infants demonstrated that blood levels following a single dose of chloramphenicol, either orally, intramuscularly or intravenously, were prolonged, detectable levels being observed for 24 to 90 hours, depending on the form of chloramphenicol used.[20, 52, 60] Sixty-five per cent of the blood level was active chloramphenicol, demonstrating the reduced rate of conversion to glucuronide in the liver of the premature and the newborn infant. Less than half of the administered dose was recovered in the urine of the newborn, with an average of only 20 per cent in the premature infant. The principal difference from adults was demonstrated to be a decrease in tubular secretion of the chloramphenicol glucuronide. In addition, a metabolic product not found in the adult was identified in neonatal urine.[5] This was a glycolytic acid amide analogue of chloramphenicol with only 4 per cent of the antimicrobial activity of chloramphenicol.

Toxicity for rats of this metabolite is of low order, the LD_{50} doses being 2950 mg. per kilogram. The toxic effect in newborn infants has been directly related to the high levels of active chloramphenicol, which accumulates in the blood stream after repeated dosage. The mechanism of action of this toxic effect is unknown. None of the newborns studied were reported to show depression of the hematopoietic system, although detailed bone marrow studies were not done in any of the infants. Toxic effects of chloramphenicol in the newborn infant can be prevented by adjusting the doses administered for the newborn's specific physiologic handicaps. A recent review of the toxicity of drugs in the neonatal period summarizes current information on this important topic.[34]

Bone Marrow Depression

Shortly after the introduction of chloramphenicol for clinical use, scattered reports associated therapy with severe depression of the bone marrow resulting in aplastic anemia or pancytopenia.[53] There is now no question that chloramphenicol can cause severe bone marrow depression with fatal outcome.[3, 4, 36] In many cases in which hematopoietic changes were noted early, discontinuing the chloramphenicol resulted in recovery within one to two weeks. The reported incidence of this complication is small, varying estimates running from 1 in 20,000 to 1 in 100,000 patients treated with chloramphenicol. It has been reported most frequently after repeated or prolonged therapy, although it has occurred after only one dose of chloramphenicol. No method is presently available to determine which patients will suffer severe changes.

Recent reports suggest that many patients on chloramphenicol treatment demonstrate hematopoietic changes which are unrecognized and reversible. Rubin and co-workers[43] have reported studies of iron metabolism in 15 adults being treated with 1 to 4 gm. daily of chloramphenicol. In 10 patients there was no effect. In five there was a delay in disappearance of radioactive iron from the plasma. No radioactive iron appeared in the circulating red cells for over eight days. The normal time of appearance is 24 to 48 hours. There was increased radioactivity over the liver in the one patient tested. One patient of the five had generalized bone marrow hyperplasia. The remaining four patients showed normal marrow. Four patients of the five showed a drop in hematocrit level which recovered when therapy was discontinued. The earliest demonstrable toxic effects on the hematopoietic system are an increase in plasma iron and in the saturation of iron-binding globulin, reflecting a decrease in the iron uptake of the erythroid tissue. The authors suggest that a determination of iron-binding capacity and plasma iron may be useful in screening patients under

therapy with chloramphenicol. In a more recent report, Saidi and Wallerstein[44] studied the bone marrow of 22 patients being treated for bacterial infections with chloramphenicol in doses of 40 to 85 mg. per kilogram per day. Twelve of these 22 had large vacuoles in the primitive erythroblasts, often associated with a fall in the circulating red cells and reticulocytes. Five of the patients were restudied one week after discontinuing chloramphenicol. The vacuoles had disappeared in all five; three of the five showed erythroid hyperplasia and reticulocytosis.

The earliest morphologic change in the bone marrow is a maturation arrest with vacuolization of the erythroid elements, associated with a drop in reticulocyte count progressing to anemia.[26, 38] Some vacuolization of the granulocytes, plasma cells and megakaryocytes follows. One patient with terminal cancer given large doses of 8 to 12 gm. daily had bone marrow depression with complete recovery on discontinuing the drug. After recovery the patient was challenged with small doses of chloramphenicol which did not cause suppression, but large doses again produced the same bone marrow effects.

The mode of action of chloramphenicol on the bone marrow is unexplained. Chloramphenicol depresses leukocyte respiration.[9] It also inhibits the synthesis of nucleic acid by normal and leukemic bone marrow cells.[58] These effects occur only at high concentrations. Unless chloramphenicol is selectively concentrated in the bone marrow, these would not be reached on therapeutic dosage. The bone marrow cells of one patient were tested after he had recovered from bone marrow depression with chloramphenicol treatment. Suggestive evidence was found of an abnormal sensitivity of nucleic acid synthesis to inhibition by chloramphenicol.

Other Toxic Manifestations

Gastrointestinal reactions such as nausea, unpleasant taste, mild diarrhea and pruritus ani occur infrequently with chloramphenicol. When they do occur, they are usually mild. Stomatitis has been reported. Overgrowth with yeast infections may occur, causing a more severe stomatitis or diarrhea.

Rare allergic reactions consist of angioneurotic edema, vesicular and maculopapular dermatitis and fever.[56] Acute necrosis of the liver has occurred after chloramphenicol therapy.[7] Peripheral neuritis associated with optic neuritis has been reported in adults and older children during prolonged administration of relatively large doses.[22] One case of acute myeloblastic leukemia has occurred after aplastic anemia.[33]

PREPARATION AND DOSAGE

Chloramphenicol can be given orally, intramuscularly, subcutaneously,

intravenously, topically and intrathecally, and is reported to be absorbed when administered rectally.

Oral Route

Two preparations are available for oral administration in children. Crystalline chloramphenicol is dispensed in capsules containing 50, 100 or 250 mg. The recommended dosage of crystalline chloramphenicol for infants over one month of age and for children is 50 to 100 mg. per kilogram given in 4 divided doses daily. With this preparation effective blood levels should be obtained within one-half hour. Delay in absorption has been noted in patients who are severely ill, particularly with signs of peripheral circulatory impairment. For these patients therapy should be started intravenously.

Because of the exceedingly bitter taste in crystalline form, a palatable suspension of the palmitic ester of chloramphenicol is marketed as Chloromycetin Palmitate, containing 125 mg. of chloramphenicol per 4 cc. After ingestion the ester must be hydrolyzed before absorption

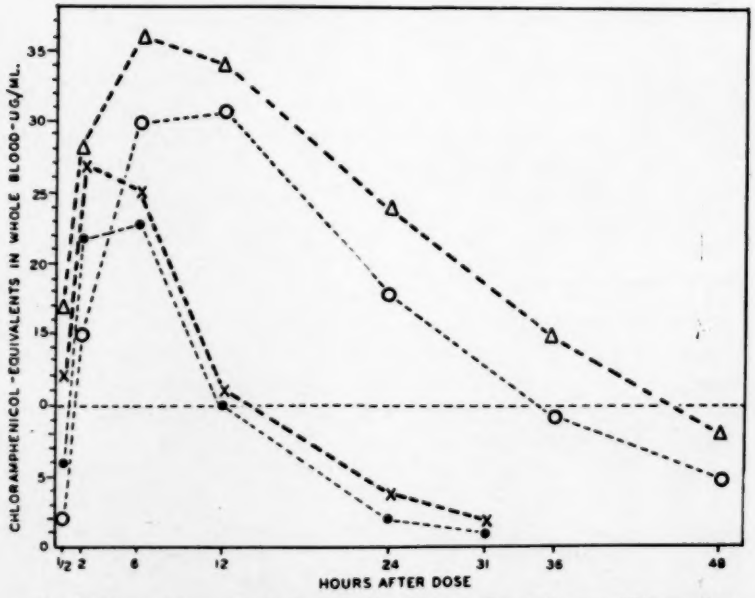

Fig. 8. Mean chloramphenicol whole blood levels, chemical assay. Chloramphenicol palmitate: O---O---O, group 1, newborn infants; ●---●---●, group 2, 11 weeks old. Chloramphenicol (crystalline): △---△---△, group 3, newborn infants; X---X---X, group 4, 4–15 weeks old. (From R. R. Storm and S. R. Ziegra: Oral Chloramphenicol in Newborn and Older Infants. *Antib. Med. & Clin. Ther.*, Vol. 8.)

occurs.[14] Consequently, therapeutic levels are not attained until two to three hours after administration. Up to 50 per cent of the dose is lost in the stool, so that dosage must be higher than with crystalline chloramphenicol: 100 to 200 mg. per kilogram per day given at 6- or 8-hour intervals is recommended.[32, 40, 47, 59] The palmitate is hydrolyzed by lipase and bile. Therapeutic blood levels have been recorded after administration to patients with fibrocystic disease and infants with diarrhea. Better absorption occurs when the drug is given to a fasting patient.

Blood levels following administration of the palmitic ester to newborn and young infants have been reported by Storm and Ziegra.[48] In newborns given 50 mg. per kilogram effective levels were present at 2 hours. Peak levels occurred between 6 and 12 hours, and therapeutic levels persisted for 24 to 36 hours. In infants one to four months of age given the same dose, faster absorption and much faster clearing were noted. The highest levels obtained were 40 gammas per cubic centimeter, and no toxicity appeared in these patients. Storm and Ziegra recommended 50 mg. per kilogram of Chloromycetin Palmitate given once every 24 hours for newborns. For infants one to four months of age the recommended dose was 50 mg. per kilogram, given every 12 hours, or a total dose of 100 mg. per kilogram per day (Fig. 8).

Parenteral Route

Two preparations are available for parenteral administration. The first is a microcrystalline powder marketed as Chloromycetin Intramuscular. A suspension for intramuscular use only is prepared by adding physiologic saline or sterile water. Because of slow absorption from the injection site, therapeutic blood levels may not be obtained for two to three hours after administration. Peak blood levels will be lower and the duration of the levels longer than with the same dose of an oral preparation. Recommended dosage for infants over one month of age and for children is 100 to 150 mg. per kilogram per day given at 12-hour intervals. This preparation should not be used to initiate treatment in seriously ill children because of the lag between administration and effective blood levels.

Chloramphenicol sodium succinate is a recently introduced ester which is highly water-soluble and hence more readily absorbed than the microcrystalline form. As Chloromycetin Succinate, it is available in sterile vials containing crystalline powder equivalent to 1 gm. of chloramphenicol, which may be dissolved in sterile water, normal saline or glucose solutions. This preparation is suitable for intramuscular, subcutaneous or intravenous use. Therapeutic blood levels are obtained within one-half hour after intramuscular administration. Peak levels

occur at one and one-half to two hours, and therapeutic levels persist for six to eight hours. Recommended dosage for older infants and children is 100 mg. per kilogram given in divided doses every 6 to 8 hours.

Blood levels have been reported following doses of 25 to 50 mg. per kilogram per day of microcrystalline chloramphenicol and chloramphenicol sodium succinate given intramuscularly to premature infants[20, 52, 60] (Figs. 9, 10). In infants under 7 days of age therapeutic blood levels were obtained with doses of 25 mg. per kilogram per day. Two therapeutic schedules have been recommended. The first is 25 mg. per kilogram of chloramphenicol sodium succinate given once daily.[20] The second is 25 mg. per kilogram of chloramphenicol sodium succinate and 25 mg. per kilogram of microcrystalline chloramphenicol given at the same time, but in separate injections, once every 48 hours.[60] Over 7 days of age these doses are inadequate to maintain therapeutic levels, and the dosage should be increased to 50 mg. per kilogram per day; 50 mg. per kilogram of chloramphenicol sodium succinate should be given once daily, or 25 mg. per kilogram of microcrystalline chloramphenicol and 25 mg. per kilogram of chloram-

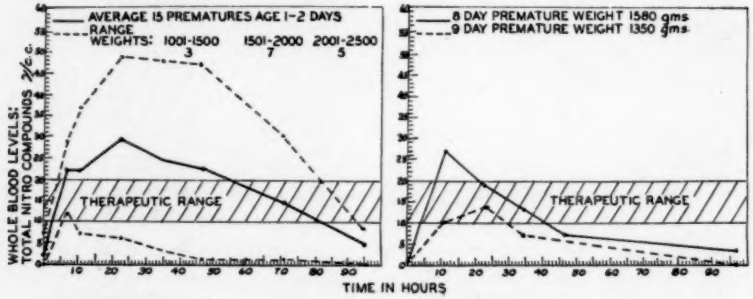

Fig. 9. Blood levels following a single dose of microcrystalline chloramphenicol, 50 mg./kg. I.M. (From J. E. Hodgman and L. E. Burns: Safe and Effective Chloramphenicol Dosages for Premature Infants. *Am. J. Dis. Child.*, Vol. 101.)

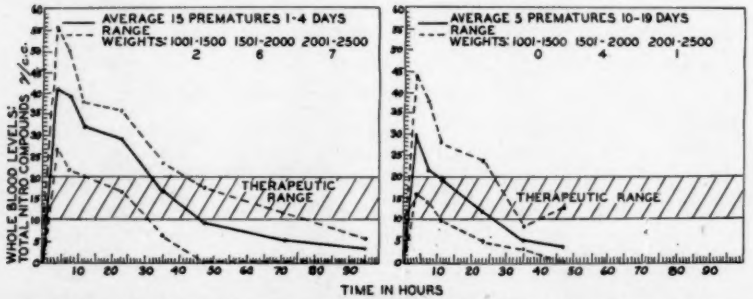

Fig. 10. Blood levels following a single dose of chloramphenicol sodium succinate, 50 mg./kg. I.M. (From J. E. Hodgman and L. E. Burns: Safe and Effective Chloramphenicol Dosages for Premature Infants. *Am. J. Dis. Child.*, Vol. 101.)

phenicol sodium succinate should be administered every 24 to 36 hours. Prematures given chloramphenicol sodium succinate intravenously maintained adequate blood levels for 24 hours after one infusion; 25 mg. per kilogram were given to infants under 7 days and 50 mg. per kilogram to those over this age. It is important to give the intravenous dose slowly over a period of three to five hours to prevent accumulation of chloramphenicol to toxic levels during administration. It must be emphasized that infants under one week of age showed greater variability of levels on a given dose than did the older prematures. Several babies under 4 days of age showed signs and symptoms of toxicity on doses of 25 mg. per kilogram per 24 hours.

The recommended dose for term infants is 50 mg. per kilogram per 24 hours administered once daily, but adequate levels have been obtained in the immediate newborn period with 25 mg. per kilogram per day.[52] We have used 50 mg. per kilogram per day in term infants without development of toxic symptoms; however, we have not treated term infants under 48 hours. Too few observations on term infants have been reported to make firm recommendations for dosage. Chemical assay for total nitro compounds utilizing capillary blood has been developed by Glazko and associates.[11] The method is a relatively simple colorimetric comparison which should be within the scope of the average hospital laboratory. Blood levels are routinely checked on all infants receiving chloramphenicol therapy in our nurseries.

Topical Administration

Several preparations are available for topical administration, including Chloromycetin cream, Chloromycetin ophthalmic ointment and drops and Chloromycetin otic drops. There would seem little indication for the use of these preparations.

INDICATIONS FOR USE

Because of its wide antimicrobial spectrum and infrequent emergence of resistant organisms, chloramphenicol is effective against many infections. Because of its toxicity for the bone marrow it is indicated only in severe infections in which it is known to be superior to other antibiotics. It is the drug of choice in typhoid fever. It has a place in the treatment of some types of meningitis and septicemia, resistant staphylococci infections and severe dysenteries. When the use of chloramphenicol is considered, the risk of the infection to the patient must be carefully weighed against the risk of the drug.

Chloramphenicol is not indicated in the majority of the acute respiratory, urinary or gastroenteric infections. In many of the reports

of fatal aplastic anemia the authors have emphasized that the indication for administration of chloramphenicol was an acute respiratory infection in which the need for any antibiotic was questionable, and certainly not one with chloramphenicol's potential toxicity.

Prophylactic use of chloramphenicol is specifically contraindicated. This is particularly true in the newborn period, in which the margin of safety between therapeutic and toxic doses is narrow. The asymptomatic infant born after prolonged rupture of the fetal membranes should not be given prophylactic antibiotics.

The indications for the use of chloramphenicol in the newborn infant are the same as those outlined for the older infant and the child, namely, severe infection not sensitive to less toxic antibiotics. Any newborn infant being treated with chloramphenicol should be carefully watched for the development of toxic symptoms and the drug discontinued promptly if these appear.

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KANAMYCIN, NEOMYCIN AND PAROMOMYCIN

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The antibiotics kanamycin, neomycin and paromomycin are all produced by soil actinomycetes belonging to the streptomyces family. Kanamycin and neomycin closely resemble each other in their chemical and physical properties, in their bactericidal action against a wide range of gram-positive and gram-negative bacteria and *M. tuberculosis*, in their pattern of absorption, distribution and excretion, and in the types, if not degree, of toxicity. Neomycin was isolated in 1949, kanamycin in 1957, and paromomycin in 1956. The indications and limitations of the first two are well understood. Although paromomycin was isolated before kanamycin, it has been studied less extensively, and less is known of its usefulness and toxicity. It has antibacterial properties similar to those of neomycin and kanamycin. Kunin and his associates[27] have demonstrated that bacteria made resistant to any one of these three antibiotics also exhibit complete cross-resistance to the other two. Kanamycin and neomycin, in spite of their valuable antimicrobial properties, are limited in their general usefulness by their nephrotoxic and ototoxic potentials. Nevertheless these very limitations may, by preventing their indiscriminate use, preserve the usefulness of kanamycin and neomycin in the management of infections due to organisms which have emerged resistant to the commonly given antimicrobial agents.

KANAMYCIN

Kanamycin (trade name Kantrex) was isolated from *Streptomyces kanamycetus* by Umezawa[35] at the Japanese National Institute of

Health and Tokyo University in 1957. It has been developed and marketed in this country by the Bristol Laboratories. It first became available for general use in 1958.

CHEMICAL AND PHYSICAL PROPERTIES

Cron and his co-workers[7] determined the chemical composition of kanamycin and showed that hydrolysis will yield 2-amino sugars linked glycosidically to 2-dioxystreptamine. The drug is water-soluble, and is stable through a pH range from 2 to 11 under normal sterilizing conditions and at a boiling temperature for 30 minutes at a pH of 6 to 8. The structural formula resembles that of neomycin, in that there is a common dioxystreptamine moiety, but the two antibiotics differ in the amino sugars.

ANTIMICROBIAL PROBLEMS IN VITRO AND IN VIVO

The antibacterial action of kanamycin is principally bactericidal.[15] Studies in vitro reveal activity against most strains of staphylococcus, vibrio, salmonella, shigella, mycobacteria, the coliform group, proteus and some strains of pseudomonas. Kanamycin is relatively inactive against streptococci, pneumococci and anaerobic organisms.[10] In its clinical use there is generally good correlation between sensitivity studies in vitro and response in vivo. Most acute infections due to kanamycin-sensitive organisms respond promptly to the administration of kanamycin, and infections due to species generally resistant are not favorably influenced by kanamycin therapy. But some striking exceptions occur in the in vitro-in vivo relationship; brucella and salmonella are quite sensitive in vitro to kanamycin, but patients with brucellosis and typhoid fever treated with kanamycin do not usually respond well clinically.[31, 32] The course of some other salmonella infections and of most shigella infections has been altered favorably by kanamycin therapy.[32] The results of the use of kanamycin in the treatment of various forms of tuberculosis have been generally encouraging.[8] Its activity appears to be about equal to that of streptomycin.

ABSORPTION, DISTRIBUTION, EXCRETION

Kanamycin is absorbed rapidly when injected intramuscularly, peak concentrations being reached within one hour.[3, 34, 39] The levels fall rapidly in 6 hours, and there is little drug in the serum 12 hours after a single injection. Most of the antibiotic is excreted in the urine within 24 hours after administration, approximately 80 per cent being excreted within the first 6 hours. There is no accumulation of kanamycin in the serum when given at 12-hour intervals to patients with normal renal function. There is little serum binding of the antibiotic, and after

parenteral administration it is excreted exclusively by glomerular filtration. It is distributed in highly vascular organs such as the liver and kidney and appears in concentrations approximately equivalent to the blood level. Penetration into spinal fluid, bone and heart muscle is poor.[34] There has been less experience with intravenous administration of kanamycin, but the pattern of distribution and excretion is the same as that following intramuscular injection.

Kanamycin is so poorly absorbed upon oral ingestion that blood levels are extremely low or nondetectable.

TOXICITY

The administration of kanamycin may be associated with two serious toxic effects and several mild side effects. The serious effects are ototoxicity and nephrotoxicity. The mild effects, which rarely interfere with its use, are eosinophilia, local pain at the site of injection, and maculopapular rashes.

During the three years kanamycin has been used, nephrotoxicity has proved to be less and ototoxicity more of a problem than was anticipated during early studies. Serious renal toxicity has been rare in adults, but acute tubular necrosis has been reported in several patients.[2] Many patients receiving kanamycin exhibit evidence of mild renal irritation as manifested by cylindruria. Nephrotoxicity has not been a serious problem in pediatric patients.[41] Cylindruria usually occurs in children when kanamycin is administered in doses exceeding 50 mg. per kilogram per day, but hematuria, albuminuria, and elevation of the blood urea nitrogen due to kanamycin virtually never occur.

Ototoxicity is the most frequent serious side effect of kanamycin therapy. Early in the laboratory studies of kanamycin, animal experiments demonstrated that the use of kanamycin could produce mild loss of vestibular function and greater loss of auditory function.[16] The principal site of involvement of the sensorineural pathway was found to be the organ of Corti.[16] The pattern of ototoxicity in human adults has been clearly defined by Frost, Hawkins and Daly.[13] In their experience, hearing for the highest frequencies was affected first, tinnitus often preceded or accompanied the onset of hearing impairment, the incidence of ototoxicity was closely related to the total dose of kanamycin administered, renal insufficiency greatly increased the probability of serious hearing impairment, and serious vestibular involvement was rare. In infants and children the pattern of ototoxicity is more difficult to define. High[17] has suggested that children may have a greater tolerance for kanamycin than do adults.

A recent study undertaken at the Houston Speech and Hearing Center indicates that kanamycin ototoxicity is closely related to the total dose administered.[42] The child with normal renal function ap-

pears to tolerate a total dose comparable to that tolerated by the adult. This allows an adequate dose and duration of kanamycin treatment for most nontuberculous infections. Age does not seem to be a factor in the incidence of ototoxicity in children, except in premature or very young full-term infants who, because of immaturity, have reduced glomerular filtration rate. Further studies of kanamycin blood levels and excretion rates are needed to establish the safe dose for these patients. Impaired renal function is an important factor in the production of kanamycin ototoxicity in any age group.[26] The use of two ototoxic drugs simultaneously should be avoided, and it is probably wise to avoid the use of two ototoxic drugs in sequence. Pretreatment and serial pure-tone testing should be performed if possible when a prolonged course of kanamycin is anticipated.

There has recently been a report of another side effect which requires further investigation. Mullett and Keats[29] observed a curare-like effect in an ether-anesthetized infant who experienced apnea after intraperitoneal instillation of 23 mg. per kilogram (75 mg.) of a 0.2 per cent solution of kanamycin. The respiratory arrest was identical to that following the intraperitoneal administration of neomycin.[9] The neuromuscular block did not respond to cholinesterase inhibitors, but was dramatically reversed by calcium gluconate.

This neuromuscular blocking effect of kanamycin had been anticipated and was studied in 1958 by Iwatsuki and his associates.[18] Using a nerve-muscle preparation in dogs, they showed that both kanamycin and streptomycin could produce a neuromuscular block with characteristics identical to those following administration of neomycin. Their work suggests that rapidity of systemic absorption rather than total dose is the critical factor in the production of neuromuscular block, that kanamycin and streptomycin are not as potent as neomycin in the production of neuromuscular block, and that neuromuscular block produced by all three drugs could be reversed by edrophonium.[8, 18, 19, 20] Timmerman and his associates[33] reported similar results. They found that polymyxin B can also produce this toxic effect. They observed that the neuromuscular block produced by neomycin and streptomycin could be reversed by neostigmine, but that that of kanamycin and polymyxin could not.

Jones[23] in 1959 described a case of neomycin-produced respiratory arrest which was improved by the use of calcium guconate. His experience prompted Mullett and Keats to use calcium in their patient. The mechanism of action of calcium is not understood.

CLINICAL INDICATIONS

The antibacterial spectrum of kanamycin makes it valuable in the treatment of infants and children with infections due to a wide range

of microorganisms. It is one of the most effective antistaphylococcal antibiotics available today.[37] As has been mentioned earlier, it is also active against most strains of *Escherichia coli*, proteus, the klebsiella-aerobactor group, and some strains of pseudomonas. Intelligent management of the patient with serious infections due to any of these organisms requires the use of antibiotic sensitivity tests as a guide to therapy. Nevertheless in fulminating infections such as are frequent in pediatric patients, empirical selection of antibiotic agents is necessary during the first 36 to 48 hours while cultures are being processed.

Kanamycin is a logical agent to use in the early management of severe infections of the newborn, since the majority of such infections are now due either to hospital strains of staphylococci or to gram-negative bacilli. In instances in which there is reasonable evidence that the infection may be due to the less commonly present pneumococcus or group A beta hemolytic streptococcus, it may be advisable to use penicillin in addition to kanamycin while bacteriologic studies are being obtained. When these studies are complete, the appropriate agent may be selected and the other discontinued. This approach is recommended for the management of septicemia of the newborn. Kanamycin is very effective in treating pneumonia, urinary tract infection, liver abscess, and peritonitis when infections in these areas are due to kanamycin-sensitive organisms.[40]

In the treatment of penicillin G-resistant staphylococcal pneumonia, kanamycin is about equal in effectiveness to the other bactericidal antibiotics (bacitracin, vancomycin, dimethoxyphenyl penicillin). But because of its greater toxicity, kanamycin may be replaced by dimethoxyphenyl penicillin (Staphcillin) in treating serious staphylococcal infections.

Kanamycin-sensitive organisms may persist when infections are in relatively avascular areas or in infections localized in abscesses or body cavities.[41] Under these conditions parenteral kanamycin therapy may need to be supplemented by surgery or local instillation of the drug. In instances of meningitis in which antibiotic sensitivity tests indicate kanamycin to be the drug of choice, intrathecal therapy should be utilized in addition to parenteral therapy.

Oral kanamycin therapy can be utilized for preoperative bowel sterilization[5] and for the management of gastroenteritis due to the pathogenic serotypes of *E. coli*.[41] It is probably equally effective as neomycin.

Because of the frequency of ototoxicity associated with long-term therapy, kanamycin is probably not indicated for treatment of patients with tuberculosis, except those who are allergic to streptomycin or those whose infecting strains are streptomycin-resistant.

Kanamycin has been used for another purpose unrelated to infectious diseases. In adult patients it has proved effective in lowering ammonia

levels in liver failure.[12] The mechanism of this action may be the reduction by neomycin of ammonia-producing bacteria in the gastrointestinal tract, but a cause-and-effect relation has not been established.

DOSAGE AND MODE OF ADMINISTRATION

Kanamycin is prepared as a sulfate. It is available in a solution for parenteral injection and in capsules for oral administration.

Kanamycin is generally administered by the intramuscular route in systemic infections. The currently recommended daily dose in the package insert is 15 mg. per kilogram per day for adults and 15 to 30 mg. per kilogram per day for children, given in divided doses every 6 to 12 hours. In severe cases these doses may be increased for short periods of time. In the adult patient the dose may be doubled, and in children it seems safe to give a dose as large as 50 mg. per kilogram per day if they have a normal glomerular filtration rate. When the larger doses are given, it is probably advisable to make the interval between doses no longer than six hours in order to maintain an even blood level and avoid excessively high peaks in blood levels. The dosage regimen currently used at Jefferson Davis Hospital, Houston, Texas, for the seriously ill child is 50 mg. per kilogram per day in 4 daily doses during the critical period, 25 mg. per kilogram per day in 2 to 4 daily doses until there is a satisfactory response of the acute phase of the illness, and 12.5 to 15 mg. per kilogram per day in 2 daily doses for a variable period of maintenance depending upon the nature of the infection. In the newborn infant or the child with known impairment of renal function the range of dosage is 10 to 25 mg. per kilogram per day divided into 2 to 4 daily doses using the smaller dose, and 4 daily doses with the larger dose. Other authorities have suggested smaller doses, as indicated in the March, 1959, News-Letter of The Committee on Control of Infectious Diseases and The Committee on Fetus and Newborn of the American Academy of Pediatrics, which recommends that the dosage of kanamycin should not exceed 2 to 4 mg. per kilogram per day for premature and full-term newborn infants.[24] Further clinical studies and blood level determination seem indicated to establish the optimal dosage in this age group.

Kanamycin can be administered intravenously, but this route should not be used except in instances in which the intramuscular route is not feasible, as in the patient with very small muscle mass or extensively damaged skin. If this route is mandatory, the drug should be given by slow intravenous infusion (60 to 80 drops per minute). The dose is 15 to 30 mg. per kilogram per day. The recommended concentration of kanamycin for intravenous use is 0.25 per cent (2.5 mg. per milliliter). This solution can be prepared by adding the contents of a 0.5-gm. vial

of kanamycin to 200 ml. of normal saline or 5 per cent dextrose in water. Chemical thrombophlebitis has not been a problem.

The oral route for the administration of kanamycin should be used only when systemic therapeutic levels are not required. It can be used as a means of preparing patients for bowel surgery, for treating ammonia intoxication due to liver failure, and for the treatment of localized enteric infections. The dose ranges from 4 to 12 gm. for adults. For children the dose is 50 mg. per kilogram per day divided into 4 to 6 doses.

Because of the difficulties associated with the sterilization of localized infections and infections in body cavities, kanamycin has been used locally to supplement its systemic administration. It has been instilled in abscess cavities, draining sinuses, the peritoneal cavity, pleural spaces and the subarachnoid space.[41] The concentration injected into the subarachnoid space has been 0.5 mg. per milliliter, and the largest daily dose has been 5 mg. Concentrations varying from 2.5 to 50 mg. per milliliter have been used in other sites. Since at least part of the antibiotic instilled locally is absorbed, the amount administered in this fashion must be taken into consideration in calculating the total and daily dose to be given to the patient.

TABLE 11. *Precautions in Use of Kanamycin in Infants and Children*

1. Careful history for renal status
2. Baseline BUN and urinalysis
3. BUN weekly and urinalysis twice weekly during therapy
4. Maintenance of optimal hydration and urine output
5. Baseline and serial audiometric studies if long-term therapy is anticipated
6. Reduction of dose in patient with altered renal function or urea retention due to other causes

NEOMYCIN

Neomycin is an antibiotic derived from a strain of streptomyces. It is marketed by several pharmaceutical firms under various trade names. Neomycin is prepared in the form of a sulfate and is a polybasic compound which is water-soluble, but insoluble in organic compounds. It is heat-stable and has remarkable stability in a wide pH range. It is active in alkaline solution and is not inactivated by gastric juice, byproducts of digestion, bacterial growth, exudates or enzymes.[1]

ANTIMICROBIAL PROPERTIES IN VIVO AND IN VITRO

In vitro, neomycin has a potent bactericidal effect against gram-positive cocci, gram-negative bacilli, acid-fast bacilli, and actinomycetes.[38] It is

more active against staphylococci than streptococci, and is active against some strains of proteus and pseudomonas. In the early years of its use (1949–52), before its toxicity limited its parenteral administration, there was a close parallel between response in vitro and response in vivo. This in vitro-in vivo relation has continued to be predictable in the oral and local uses of neomycin.

Bacterial resistance to the drug may be induced in vitro, but the emergence of bacterial resistance in the individual case during a single course of therapy has not been a problem clinically.

ABSORPTION, DISTRIBUTION, EXCRETION

Neomycin is readily absorbed after intramuscular injection. Therapeutic blood levels and tissue levels are maintained for 6 to 10 hours after a single injection. The drug is excreted principally in the urine. Accumulation occurs in patients with impaired renal function, and even patients with normal renal function may excrete neomycin for 24 hours after its discontinuation.[27]

Neomycin is poorly absorbed from the gastrointestinal tract.[1] About 97 per cent of the administered oral dose is excreted unchanged in the feces. Little can be found in blood or tissues, and only 3 per cent or less has been recovered in the urine. The only exceptions to this occur in patients with hepatic insufficiency associated with renal insufficiency,[25] and perhaps in patients with intestinal obstruction and very young infants who receive large doses or oral neomycin.

There is no demonstrable absorption of neomycin applied topically to the skin or mucous membranes. There is probably considerable absorption, however, when neomycin is instilled into body cavities.[9]

TOXICITY

The systemic use of neomycin is sharply limited by its toxicity. Its toxic properties were recognized early in its investigation, but it has been used during the last 12 years in selected cases in which the patient's life depended upon its use, the risk of using the drug being weighed against the risk of the illness.

It is ototoxic and nephrotoxic.[36] The ototoxicity is insidious. It may come on abruptly without the warning signs of vertigo or tinnitus, or it may be delayed, having its onset one or two weeks after discontinuation of the drug. The frequency and severity of hearing loss would seem to be greater than that induced by kanamycin, but proof of this awaits further definitive studies with kanamycin. The nephrotoxicity is unquestionably greater than that produced by kanamycin. This nephrotoxicity in turn, by diminishing excretion of drug, may well increase the possibility of the development of eighth nerve damage. Since kana-

mycin can be given for any disease state in which parenteral neomycin is indicated and since kanamycin appears at present to be less toxic, it would seem that parenteral use of neomycin should be discontinued.

Neomycin used orally may have undesirable side effects. It has a laxative effect, it produces alteration in bacterial flora of the gastrointestinal tract which may result in superinfection due to *Candida albicans*, and recently a malabsorption syndrome resulting from oral administration has been described.[21] An experimental malabsorption syndrome was induced by giving large doses of neomycin orally to adult patients without known gastrointestinal disease. The dose given in this study was 12 gm. daily divided into 3 doses. The weights of the patients were not given, but assuming 70 kg. as the average adult weight, this dose would be approximately 170 mg. per kilogram per day. In order to characterize the effect of neomycin upon intestinal absorption, six absorptive parameters were utilized: plasma carotene, urinary D-xylose excretion, serum cholesterol, plasma iron-59 curves, glucose tolerance, and urinary excretion of CO^{60}-labelled vitamin B_{12}. Results showed a decrease in plasma carotene concentration, decreased iron-59 absorption curves, decreased urinary excretion of CO^{60}-labelled vitamin B_{12}, decreased urinary excretion of D-xylose, flattened glucose tolerance curves, and a fall in serum cholesterol which was probably significant. These findings indicate that neomycin in large doses is capable of producing a broad spectrum of malabsorptive errors comparable to those in idiopathic steatorrhea. This study has been reported in some detail here because of its applicability in the pediatric management of gastroenteritis.

There is one other uncommon but important toxic effect of neomycin. As has been mentioned on page 1046, neomycin administered intraperitoneally and intrapleurally can produce respiratory arrest or insufficiency.[9] This complication has been observed in at least 18 patients, 17 of whom received the drug intraperitoneally and one intrapleurally. Eleven of the 18 patients were children. It has been suggested that this may occur more frequently in children because of the danger of relative overdosage. Development of respiratory arrest is also thought to be augmented by inflammation of peritoneum resulting in rapid systemic absorption. Animal investigations have shown the pharmacologic mechanism in neomycin apnea to be the result of a generalized neuromuscular block identical to that produced by d-tubo-curarine.[19, 33] This block is potentiated by ether and antagonized by the cholinesterase inhibitors neostigmine and edrophonium.

CLINICAL INDICATIONS

Neomycin should probably not be used parenterally for treatment of systemic disease because of its toxicity and because less toxic drugs are

available for the same purposes. The principal uses of neomycin are locally as a topical solution or ointment for superficial infections, orally for preoperative bowel preparation, in the management of liver failure and for the management of gastroenteritis due to the pathogenic serotypes of *E. coli*. In pediatric practice the last is its most important use. Several new developments justify some discussion of this use.

Treatment of Pathogenic Escherichia Coli Diarrhea. Neomycin sulfate administered orally in doses of 50 to 100 mg. per kilogram per day for a period of 10 days has been a fairly standard treatment for pathogenic *E. coli* diarrhea during the last decade.[30] Since this is a disease characterized by clinical and bacteriologic relapses, it has been difficult to define sharply the efficacy of the drug, but in general, neomycin has seemed useful both in the management of the individual patient and in the control of hospital spread of this infection. The drug has been administered to several groups of patients and personnel harboring *E. coli*: the patient with proved pathogenic *E. coli* diarrhea, the patient admitted to the hospital with gastroenteritis which is likely to be due to pathogenic *E. coli*, the inapparent patient-carrier who has to be housed with susceptible infants, and personnel carrying pathogenic strains during an epidemic period. Under certain circumstances all these uses of neomycin are justified. But in areas where large amounts of neomycin or kanamycin or both have been used, periodic evaluations are needed to see whether neomycin-resistant strains of pathogenic *E. coli* have emerged. It has been reported that *E. coli* 0111:B_4 has acquired neomycin resistance throughout France.[28] Recent clinical experiences and laboratory tests indicate that this situation may be occurring in Houston and its environs.

In addition to an awareness of the possibility that a patient's lack of improvement on neomycin therapy may be due to resistance of the etiologic agent to the antibiotic, the possibility must be kept in mind that the lack of improvement may be due to production of a malabsorption syndrome by the antibiotic. This syndrome has persisted in adults for as long as five days after discontinuation of neomycin.

The question of the emergence of neomycin-resistant strains of *E. coli* and the importance of the malabsorption syndrome need further study, but at present neomycin is still an important drug in the treatment and prevention of gastroenteritis due to pathogenic *E. coli*.

DOSE AND ROUTES OF ADMINISTRATION

Neomycin sulfate is available as a powder, in 0.5-gm. tablets, and in ointments containing 5 mg. per gram. The concentration used for solutions is 5 mg. per milliliter.

The oral dose of neomycin for adults for intestinal antisepsis before bowel surgery is 1 gm. every hour for 4 doses, then 1 gm. every 4 hours

for one to three days. The oral dose generally recommended for the treatment of enteric infections in infants and children is 50 to 100 mg. per kilogram per day for 7 to 10 days.[80] The dose recommended by the manufacturer is smaller, 30 to 60 mg. per kilogram per day. The treatment of personnel harboring pathogenic *E. coli* during epidemic periods poses a problem. The dose given in Houston has been 50 mg. per kilogram per day for 5 to 7 days. Larger doses have produced diarrhea and symptoms of gastritis.

PAROMOMYCIN

Paromomycin (trade name Humatin) is a new antibiotic isolated from a strain of streptomyces. Microbiological studies reveal that paromomycin has bacteriostatic and bactericidal activity against gram-positive and gram-negative bacteria, and *M. tuberculosis*.[4, 11] It is also antiprotozoal, being active against amebae and trichomonads.[4] In clinical use the antibiotic is limited by its toxicity. Animal experiments performed by the Research Division of Parke, Davis and Company showed paromomycin to be nephrotoxic when administered parenterally. Preliminary tests for ototoxicity in cats showed no evidence of damage to the inner ear. Insufficient tests were performed to eliminate the possibility that this toxic effect might be associated with the parenteral use of the drug. Because of the potential nephrotoxicity of paromomycin when given parenterally, it is used only in the oral, nonabsorbable form.

Results of clinical studies using paromomycin in the treatment of intestinal amebiasis and enteric bacterial infections[6] are now available. Paramomycin appears to be a suitable treatment for chronic and acute intestinal amebiasis. Patients with gastroenteritis due to shigella, salmonella and various pathogenic serotypes of *E. coli* have been treated with paromomycin. Results were satisfactory, but the drug does not appear to have any particular advantage over other antibiotics in the management of bacterial enteritis.[14]

Paromomycin may also be used for the preoperative suppression of bowel flora and for the management of hepatic coma.

Paromomycin is available only in the form of capsules containing 250 mg. of paromomycin sulfate. The recommended oral dose of paromomycin for bacillary enteric infections is 35 to 100 mg. per kilogram per day in divided doses at 6- or 8-hour intervals up to 7 days. The usual dose for children is 50 mg. per kilogram per day. For the treatment of amebiasis in children the recommended dose is 22 mg. per kilogram per day in divided doses at mealtimes for 5 days. In adults the recommended dose for amebiasis is 0.75 to 1.5 gm. daily in divided doses. The dose used in hepatic coma is 6 gm. per day in divided doses.

The only side effect observed in the use of paromomycin is a mild laxative effect.

TABLE 12. *Daily Doses of Kanamycin, Neomycin and Paromomycin Recommended by Manufacturers*

INDICATION	KANAMYCIN	NEOMYCIN	PAROMOMYCIN
Systemic infection:			
Adults	15 mg./kg.		
Children	15–30 mg./kg.		
Intestinal sterilization:			
Adults	3–4 gm. x 4 days	6 gm. x 1 day	2 gm. x 4 days
Children			
Hepatic coma:			
Adults	4–12 gm.	8–12 gm.	6 gm.
Children			
Amebiasis:			
Adults			0.75–1.5 gm.
Children			22 mg./kg.
Intestinal infection:			
Adults	3–4 gm.		35–50 mg./kg.
Children	50 mg./kg.	30–60 mg.	50–100 mg./kg

SUMMARY

1. Kanamycin, neomycin and paromomycin have virtually identical antibacterial spectra with complete crossover in sensitivity and resistance. They are active against staphylococci, *E. coli*, the klebsiella-aerobacter group, most strains of proteus and some strains of pseudomonas. They are relatively inactive against streptococci, pneumococci and anaerobic organisms. They are about equal quantitatively in their bactericidal activity.

2. Although there is little published information about the pharmacology of paromomycin, all three antibiotics seem to be similar in their absorption, distribution and excretion. None of these drugs is significantly absorbed when given orally, but with renal insufficiency there may be sufficient delay in excretion to produce toxic blood levels.

3. The nephrotoxic effects of all three drugs and the ototoxic effects of kanamycin and neomycin are qualitatively similar, but there are quantitative differences. Kanamycin seems to be the least toxic of the three and consequently is the only one which should be administered systemically. In addition to nephrotoxicity and ototoxicity, the systemic administration of kanamycin may be associated with skin rashes. The oral administration of all three agents may produce diarrhea.

4. All three drugs have been used orally in the treatment of enteric infections due to susceptible organisms, in the preparation of the bowel for surgery, and in the management of hepatic coma. Paromomycin is more active against amebae than neomycin and has been recommended for the treatment of intestinal forms of amebiasis.

5. Kanamycin is the preferred drug in the treatment of systemic infections and is generally effective in infections due to susceptible organisms. Its most valuable use has been in the treatment of staphylococcal and proteus infections, and it has been the most effective drug available in the treatment of some other gram-negative bacillary infections. When a patient fails to respond to the administration of one of these three drugs, there is no advantage to giving another by the same route because of the crossover in their antibacterial activity.

6. The usual parenteral dose of kanamycin is 15 to 50 mg. per kilogram per day, but lower doses should be used in patients with delayed renal excretion. The concentration of kanamycin and neomycin for local use is 2.5 to 5 mg. per milliliter. The daily oral dose of all 3 drugs varies from 22 to 100 mg. per kilogram, lower doses being used in intestinal infections and higher doses in bowel sterilization and the treatment of hepatic coma.

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POLYMYXIN, COLISTIN AND BACITRACIN

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Five years ago the applied pharmacology of polymyxin and bacitracin was reviewed.[8, 9] The fundamental information on the pharmacologic properties of these agents has changed very little. Nevertheless the position of these drugs in the medical armamentarium must be re-evaluated because of changes in the pattern of microbial disease and the advent of new drugs.

Bacitracin and the polymyxins (including colistin) are peptide drugs of relatively large molecular size, poor diffusibility and significant toxicity. For these reasons their indications, dose and route of administration need to be more sharply defined than those of some other antimicrobial drugs for which "general usefulness" is claimed.

POLYMYXIN

The role of the polymyxins has increased in importance during the past few years, in proportion to the increased prevalence of drug-resistant gram-negative bacteria encountered in medical practice, particularly in hospitals. In a summary prepared 10 years ago[6] I pointed out that *Pseudomonas aeruginosa* could be called an "opportunist" in that it rarely produced primary infections, but frequently complicated pre-existing disease. The class of gram-negative "opportunists" has broadened in the last decade partly because of the greatly increased number of debilitated patients in hospitals and partly because of the

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partial suppression of normal flora by the high concentration of antimicrobial drugs in that environment. A majority of such bacterial infections acquired in hospitals are caused by gram-negative enteric bacteria (*E. coli, A. aerogenes, Pseudomonas aeruginosa, Proteus sp.*, and so on) which often are resistant to the commonly given antimicrobial drugs. This emphasizes the usefulness as well as the limitations of drugs of the polymyxin group.

The polymyxins (A, B, C, D, E) are a group of basic polypeptides with a molecular weight of about 1100. They contain various amino acids in addition to a C_9 fatty acid, d-6-methyloctan-1-oic acid.

Polymyxins are stable as acid salts, even in solution, for long periods. The infra-red absorption spectrums of individual polymyxins are characteristic.

Because of nephrotoxicity the use of polymyxins A, C and D has been abandoned. Only polymyxin B is presently used in clinical medicine. Colistin belongs in the group of polymyxins and is either identical with, or closely related to, polymyxin E.[20] Commercial preparations of polymyxin B are 65 to 75 per cent pure. The unit of polymyxin B is based on a theoretical potency of 10,000 units per milligram of the pure drug. Thus 1 microgram equals 10 units. The drug is distributed in terms of units and "equivalent weight" of the pure material, in dry form. It is readily soluble in water or physiologic salt solution up to concentrations of 25 mg. per milliliter.

ANTIMICROBIAL ACTIVITY

The polymyxins are selective antimicrobial substances specifically active against gram-negative rods, including *Pseudomonas aeruginosa.* Most strains of that organism are inhibited in vitro by less than 8 micrograms per milliliter. Proteus species, however, are often resistant to polymyxins.

Polymyxins are strongly bactericidal substances which act by disrupting the osmotic characteristics of the bacterial cell wall onto which they have become adsorbed. This increases the permeability of the cell wall so that cellular constituents, particularly purines and pyrimidines, escape into the environment. Actual lysis has been observed with a few bacteria.

Resistance to polymyxins emerges infrequently in most microbial species, but occasional resistant strains are encountered among susceptible species. There is complete cross-resistance between polymyxins B and E and colistin, but no cross-resistance with other clinically used antibiotics.

Because of their limited antibacterial spectrum, polymyxins are often combined with other drugs for topical application. Thus polymyxin B

is combined with bacitracin or neomycin in a large variety of topical preparations designed to suppress mixed bacterial surface infections of skin, mucous membranes, eye, ear, and so forth. In such drug mixtures each agent acts on a separate portion of the microbial population.

Polymyxin can sometimes participate in combined antibiotic action which results in true drug potentiation against a single microbial species. This can be observed frequently in vitro, tetracyclines or chloramphenicol acting simultaneously with polymyxin B against Pseudomonas or coliform organisms. Such synergistic action can be used to advantage clinically, because it makes possible the use of small doses of polymyxins for long periods in conjunction with other drugs, whereas such small amounts of polymyxins used alone might be inadequate for therapy.[7]

TOXICITY

When polymyxin B is applied to skin, mucous membranes, or granulating or denuded surfaces, when aerosols are inhaled, or drug is ingested, so little drug is absorbed that toxicity may be disregarded. In concentrations of 1 mg. per milliliter of solution or per gram of ointment the drug is virtually nonirritating. When polymyxin is administered parenterally, the undesirable effects are well defined and fall into the following categories.

Local Pain at Site of Injection. After intramuscular injection there is often transient local pain which can be readily prevented by the presence of a local anesthetic in the drug solution. About 40 to 70 minutes after the injection a "drawing," "aching" pain sensation returns, often radiating peripherally in the sensory nerve distribution. This may persist for several hours and cannot be prevented by the local anesthetic. The latter pain varies greatly in frequency and severity among patients and from day to day in the same person, and tends to be minimal in children. It can be largely prevented by forming a complex of polymyxin with methane sulfonate. From such a complex active drug is released very slowly, and thus the local irritating effect appears to be minimized. A more direct approach would be the administration of the polymyxin by the intravenous route instead of the intramuscular one. When it is given intravenously in a very slow drip, there is no local irritation or pain whatever.[5] We have encountered no definite contraindications to this route, although, of course, neurotoxicity and nephrotoxicity can occur in the same degree as with intramuscular injection.

Neurotoxicity. After intramuscular or intravenous injections of doses which result in serum levels of polymyxin in excess of 1 or 2 micrograms per milliliter, there is often flushing of the face, dizziness.

progressing with increasing dosage to demonstrable ataxia, drowsiness and a variety of peripheral sensory disturbances. Most common among the last are paresthesias of circumoral and stocking-glove distributions. The intensity of these effects varies in different persons and is regularly related to concentration of circulating drug. These effects are therefore minimal if drug is slowly absorbed (e.g. from the methane sulfonate complex) and excreted at a normal rate. Conversely, they are magnified in severity if excretion is impaired because of renal insufficiency with nitrogen retention. All these neurotoxic signs disappear when the drug has been completely excreted. Sequelae have not been encountered.

The intrathecal injection of polymyxin B in daily doses of 5 mg. or less for adults is rarely accompanied by symptoms suggesting direct irritation of meninges. With higher doses (5 to 10 mg. daily), however, there may be meningeal irritation with headache, stiff neck, pleocytosis and increased protein content of the cerebrospinal fluid, and fever. All these signs may be minimized by spacing intrathecal injections two or three days apart, and they all disappear soon after drug administration is stopped. Doses greater than 10 mg. daily should *never* be injected intrathecally because they have been reported to produce serious effects on the central nervous system.

Nephrotoxicity. With proper knowledge and experience the nephrotoxic potential of the polymyxins need never preclude their use when they are indicated in patients with adequate renal function. At parenteral dose levels of 2.5 mg. per kilogram per day, or more, there frequently develops proteinuria, cylindruria and hematuria. With doses above 3 mg. per kilogram per day nitrogen retention develops frequently and the glomerular filtration rate diminishes. These disturbances of renal function tend to increase with the duration of administration of polymyxins. They are reversible, however, if treatment is short and there is no established need for such large doses. In patients with normal renal function the administration of 2.2 mg. per kilogram per day, or less, for 2 weeks is not accompanied by significant nephrotoxicity. At times such dosage may be tolerated for long periods, e.g. 355 days.[19]

In patients with pre-existing significant impairment of kidney function much greater caution is necessary, because in them doses of 1.5 mg. per kilogram per day of polymyxins, or even less, may result in additional depression of renal function. Such patients should receive parenteral (intramuscular or intravenous) polymyxins only if good laboratory control of renal function is available, and their dose should be limited to 1.0 to 1.5 mg. per kilogram per day for 5 to 10 days.

Other Side Effects. Fever and a variety of skin eruptions have been observed occasionally. They disappear promptly when administra-

tion of parenteral polymyxins is discontinued. Allergic sensitization appears to be rare.

ADMINISTRATION AND DOSAGE

Topical Administration. Solutions or ointments containing approximately 1 mg. of polymyxin B per milliliter or gram can be applied to infected surface lesions of skin, mucous membranes, wounds, burns, conjunctiva or external ear. Many different preparations are available, all of which take advantage of the fact that high concentrations of polymyxin B are stable and poorly absorbed, and have great antibacterial efficacy against gram-negative organisms with which intimate contact can be established. Such preparations are less effective if excessive exudate or pus is present. Sterile solutions of polymyxin B, 1 mg. per milliliter, may also be instilled into pleural or joint spaces after appropriate drainage of suppuration, particularly in infections of these spaces with *Pseudomonas aeruginosa*. Destructive infections of the cornea caused by the same organism may be treated by subconjunctival injection of polymyxin B up to 20 mg. per day.

Intramuscular or Intravenous Injection. Polymyxin B is available as a sterile powder in 50-mg. (500,000 units) amounts in multiple-dose vials. For intravenous injection the material is dissolved in 200 milliliters, or more, 5 per cent dextrose in water and administered by continuous drip. For intramuscular injection 50 mg. are dissolved in 2 ml. of isotonic salt solution containing 2 per cent procaine, and appropriate amounts are injected deeply into gluteal muscles. The dissolved material may be stored in the refrigerator for several weeks. In patients with relatively normal renal function the daily dose should be 2.5 mg. per kilogram. In those with pre-existing kidney impairment it should be 1.5 mg. per kilogram, or less, and treatment must be guided by frequent laboratory checks on some measure of nitrogen retention. The total daily dose is administered either by continuous intravenous drip, or by four equal intramuscular injections at six-hour intervals.

Intrathecal Injection. In meningitis caused by *Pseudomonas aeruginosa*, and occasionally by other gram-negative bacteria which are resistant to most drugs, intrathecal administration of polymyxin B is the treatment of choice. The sterile powder is dissolved in sterile physiologic salt solution to give a final concentration of 0.5 mg. per milliliter. The dose for children under 2 years is 2 mg. in a single intrathecal injection, for older children 5 mg., and for adults 5 to 10 mg. After daily injections for three to five days the drug should be given every other day in the same dosage for three weeks, or for at least two weeks after cultures of the cerebrospinal fluid have been negative and the sugar content has returned to normal (see Fig. 11). There is no

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demonstrable benefit from intramuscularly administered polymyxin in Pseudomonas meningitis, and nothing is gained by adding intramuscular drug while administering intrathecal polymyxin.

ABSORPTION, DISTRIBUTION AND EXCRETION

After topical administration or ingestion of polymyxin there is so little absorption that no drug can be found in blood or urine. After intramuscular or intravenous injection of 2 mg. per kilogram per day serum levels of 1 to 5 micrograms per milliliter are attained. Blood-borne polymyxin reaches parenchymatous organs, but the drug does not pass readily into pleural or joint spaces, or into the central nervous system and the cerebrospinal fluid. In order to achieve therapeutically effective concentrations in those areas the drug must be injected intra-articularly, intrapleurally or intrathecally. In spite of adequate diffusion the therapeutic activity of polymyxin in parenchymatous organs is limited, because the drug appears to combine with tissue constituents, particularly polyphosphates. Thus bacteria lodged in organ tissues often survive in the presence of the drug.

Absorbed polymyxin is excreted largely in the urine. Levels of 10 to 160 micrograms of polymyxin per milliliter can be found. The antibacterial effect of these high concentrations in the urine is of great therapeutic benefit in infections of the urinary tract caused by gram-negative bacteria resistant to most other antimicrobial agents.

CLINICAL USE

The polymyxins are most effective as therapeutic agents when significant concentrations of drug can be in direct contact with susceptible gram-negative organisms at the site of their multiplication, without having to pass tissue barriers. Thus the polymyxins are well suited for treatment of gram-negative bacterial infections which are limited to surfaces (e.g. eye, ear, skin, wounds, burns) or body spaces (e.g. joint, pleural, dural), but commonly fail to eliminate infections involving parenchymatous organs (e.g. salmonellosis). Bacteremia without involvement of deep tissues may respond to the blood levels achieved by intramuscular or intravenous injection of polymyxins. Because polymyxins are excreted in the urine in high concentration, they are suitable for the suppression of gram-negative bacteria causing urinary tract infections.

Among the infectious organisms susceptible to polymyxins, *Pseudomonas aeruginosa* occupies a special place. Not only is it commonly resistant to most other drugs, but also it tends to cause infectious processes limited by tissue barriers and often fails to invade parenchymatous organs. Thus it is singularly well suited to therapy with

polymyxins. The increasing importance of Pseudomonas infections has been reviewed by Forkner.[3] Although Pseudomonas is often called an "opportunist," it may cause disease marked by chronicity, severity and mortality (particularly in debilitated persons) unless it is adequately treated.

The polymyxins have been found most useful in the treatment of the following clinical situations:

URINARY TRACT INFECTIONS. In infections of the urinary tract caused by microorganisms resistant to commonly given antimicrobial drugs, particularly *Pseudomonas aeruginosa*, polymyxins are the drugs of choice. Full systemic doses (2.0 to 2.5 mg. per kilogram per day) should be given for 7 to 10 days by intermittent intramuscular or continuous intravenous injection. This is particularly valuable in acute pyelonephritis, representing a first attack, rather than a recurrence of previously established infection, and often leads to true cure. In chronic pyelonephritis this form of treatment often suppresses bacteriuria or the clinical signs of activity, but it rarely eradicates the infection.

BACTERIAL MENINGITIS. In bacterial meningitis caused by *Pseudomonas aeruginosa* and certain other gram-negative bacteria which are resistant to other antimicrobial drugs, polymyxins may be the drugs of choice. Treatment in such cases must be based on an etiologic diagnosis with demonstration of the microorganism in the laboratory. Meningitis caused by Pseudomonas often gives a picture of slowly progressing, indolent inflammation of the meninges, and a high index of suspicion is required for making an early diagnosis by laboratory methods.[2, 3, 6] This clinical picture is associated with exquisite localization of the microorganisms in superficial layers and on the surface of meninges bathed by cerebrospinal fluid. Systemically administered polymyxins do not reach the cerebrospinal fluid in significant concentration, and it is therefore essential that intrathecal polymyxin be administered in proper dose for a sufficient time to eradicate the organisms. The drug is injected intrathecally (2 mg. in infants up to 2 years, 5 mg. in older children, 5 to 10 mg. in adults) daily for 3 days, then on alternate days for the remainder of 3 weeks. If the intrathecal polymyxin does not exceed a concentration of 0.5 mg. per milliliter, there are usually no side effects, or at most transient headache, fever, or pleocytosis of the cerebrospinal fluid. It is unnecessary to give systemic polymyxins together with the intrathecal regimen. An example of such therapy is shown in Figure 11.

A 2½-year-old girl sustained skull fractures in the course of an automobile accident. After cleansing and débriding her scalp wounds and treatment of shock, burr holes were made in the skull. During surgical manipulation cerebrospinal fluid escaped into the wound. In the postoperative period fever, leukocytosis, and stiffness of neck developed, and cultures of the cerebrospinal fluid, as well as of the scalp wound, revealed *Pseudomonas aeruginosa*. The parenteral administration of antimicrobial drugs failed to influence the clinical course until intrathecal injection of polymyxin B, 5 mg., daily

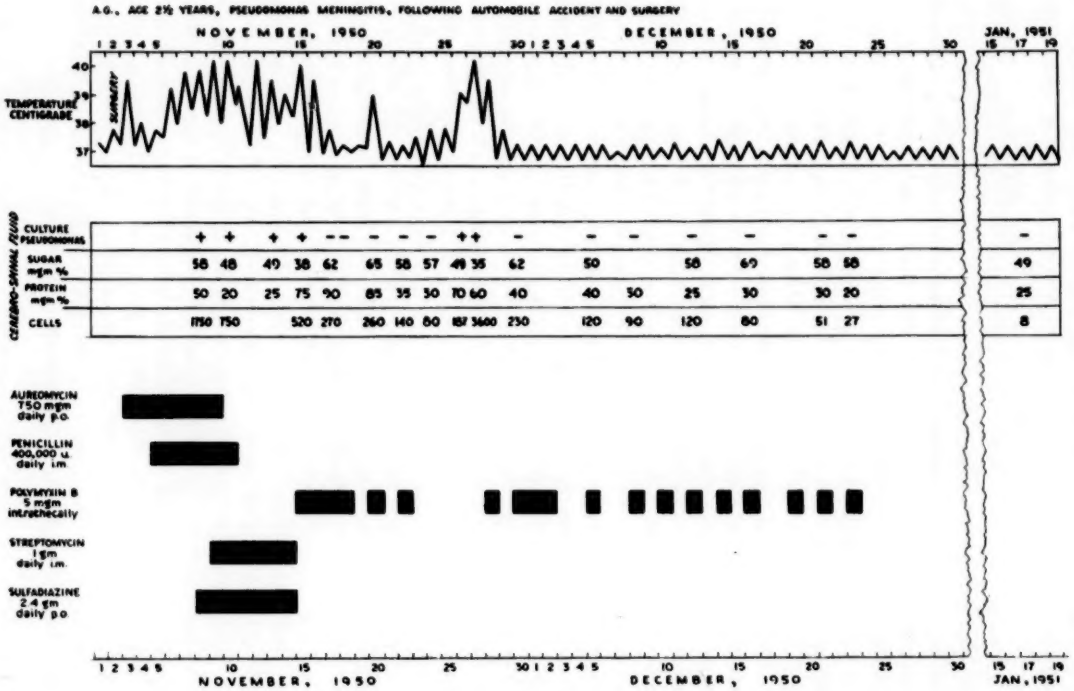

Fig. 11. Pseudomonas meningitis treated with intrathecal polymyxin B.

was started. This was followed by prompt and dramatic improvement in symptoms and signs. When intrathecal polymyxin was stopped after one week, the patient relapsed clinically and Pseudomonas again grew in cultures of the spinal fluid. A subsequent three-week course of intrathecal polymyxin resulted in permanent cure.

Bacteremia. Bacteremia caused by enteric gram-negative organisms occurs with relative frequency in patients receiving high doses of corticosteroids, metabolic antagonists, and other chemotherapeutic substances for neoplastic or chronic degenerative diseases. Bacteria such as Pseudomonas may occasionally be eliminated from the blood stream by systemically administered polymyxins, but if parenchymatous organs are involved, infections cannot be eliminated. Similarly, bacterial endocarditis caused by Pseudomonas *cannot* usually be cured by polymyxins unless surgical removal of infected tissue, clot or vegetation is possible.[18]

Local Infections of Skin, Mucous Membranes, Eye, Ear. Pseudomonas and other gram-negative bacteria are often part of the mixed flora in such infections. They can be effectively suppressed by polymyxins administered topically as creams, sprays, solutions, available in a multitude of preparations, usually in combination with other antimicrobial drugs. External otitis is often associated specifically with Pseudomonas infection, and responds to topical polymyxins. Pseudomonas ulcer of the cornea is best treated by topical and subconjunctival application of these drugs (up to 20 mg. of polymyxin B injected daily).

Enteric Infections. Although salmonella infections fail to respond to polymyxins, strictly local bacterial enteritis associated with shigella, enteropathogenic *E. coli*, Proteus or Pseudomonas, particularly in small children, can be treated effectively by the oral administration of 15 to 20 mg. per kilogram of polymyxin B for 5 to 20 days. This treatment has the advantage that it affects only the gram-negative portion of the intestinal flora and thus rarely induces diarrhea or other side effects. Conversely, polymyxins cannot be given by themselves for preoperative suppression of bowel flora.

Tracheobronchial Infections and Pneumonia. In children with cystic fibrosis (mucoviscidosis) or bronchiectasis and in patients confined to respirators, Pseudomonas infection of the respiratory tract occurs. Inhalation of aerosols containing polymyxin has suppressed the organisms in some cases. Solutions for nebulizers should contain 1 to 10 mg. of polymyxin per milliliter, and 2 ml. of such solutions should be inhaled 6 to 8 times daily.

COLISTIN*

Colistin is a drug currently advertised as "an entirely new antibiotic."

* The observations on colistin made in the author's laboratory were aided by a gift from the Warner-Lambert Research Institute. Supplies of drug were received through Dr. J. J. Pepper.

It was discovered in 1950 by Koyama et al. [12] According to experts of the Food and Drug Administration, "Colistin resembles the polymyxins and circulin in its structure. . . . While some differences were noted between colistin and polymyxin E their contents of L-leucine and L-threonine were not sufficiently at variance to establish that the two are in fact different."[20]

The antibiotic spectrum of colistin is identical with that of polymyxins, and there is complete cross-resistance between these agents. Most investigators have found no significant quantitative difference in the antibacterial activity of colistin and polymyxin B.[4, 13, 14, 16, 17] One article[15] describing significantly greater activity of colistin against Pseudomonas and other gram-negative bacteria is extensively reproduced in advertising. That study, however, compared *colistin sulfate* with polymyxin B, not colistin methane sulfonate used clinically. For the time being it is proper to regard colistin as one of the polymyxins, similar to (and perhaps identical with) polymyxin E.

Colistin is available commercially as the sodium salt of the methane sulfonate base in sterile vials containing 150 mg. of the drug together with a local anesthetic and buffer. The material is readily soluble in water. The recommended daily dose is 1.5 to 5.0 mg. per kilogram, injected intramuscularly in 2 to 4 divided doses.

ABSORPTION, EXCRETION AND TOXICITY

Polymyxins form complexes with methane sulfonate from which the chemotherapeutically active molecule is released slowly. This slow release minimizes local and radiating pain and tends to reduce fluctuations between high and low blood levels by creating a "depot" of drug. As the neurotoxic and nephrotoxic effects of polymyxins are largely a function of blood levels, the methane sulfonate complexes of colistin, or of polymyxin B, appear to be significantly less toxic than the soluble sulfates. During 6 hours after intramuscular injections of 30 mg. of colistin methane sulfonate drug concentrations averaged from 1.4 to 1.9 micrograms per milliliter of serum and from 2.6 to 3.6 micrograms per milliliter of urine.[14] A large proportion of intramuscularly injected colistin was excreted in the urine. After intramuscular injection of 130 mg. of colistin methane sulfonate every 6 hours the urine of patients with urinary tract infections contained from 2 to 32 times the concentration of drug necessary to inhibit the infecting organism in vitro.[13] Thus it appears that in spite of delayed absorption colistin concentrations in urine can be adequate to suppress sensitive microorganisms.

The neurotoxic effects of colistin appear to be identical with those of other polymyxins, but in keeping with delayed absorption and lower drug levels, these side effects are less intense. A similar explanation may

account, in part, for the lower incidence and lesser severity of nephrotoxic effects with colistin methane sulfonate than with polymyxin B sulfate.[13, 16] Preliminary observations with polymyxin B methane sulfonate suggest that its absorption, excretion and toxicity may parallel those of colistin methane sulfonate. Thus the nature of the complex rather than that of the active molecule may determine pharmacologic behavior of these substances.

CLINICAL USE

The general indications for the use of colistin parallel those for other polymyxins. Their most important use will undoubtedly be in urinary tract infections, in which encouraging results have been obtained[13, 14, 15] comparable to those reported during the last decade with other polymyxins. For adequate urine levels the intramuscular injection of 100 to 150 mg. of colistin every 6 hours will be required in adults. The effect of colistin in bacteremias caused by gram-negative bacteria is equivocal, as described for other polymyxins. Like other polymyxins, colistin failed to cure endocarditis.[14]

The systemic administration of colistin had no effect on the development of Pseudomonas meningitis[14] as described above for systemically administered polymyxins. Intrathecal injection of colistin for bacterial meningitis has not been reported and would not appear advisable.

Colistin administered by the oral route is absorbed only to a negligible extent and largely excreted in the feces. Oral colistin in a daily dose of 15 mg. per kilogram has been given successfully in small children with bacterial gastroenteritis associated with certain *E. coli* serotypes, but was found inferior to polymyxin B in shigella enteritis.[16]

The definitive place of colistin in the medical armamentarium must await its comparison with polymyxin methane sulfonate and further studies on the clarification of its similarity to polymyxin E.

BACITRACIN

Discovered in 1943 by Johnson et al.[11] as a product of the "Tracy" strain of *Bacillus subtilis*, bacitracin was originally proposed as a therapeutic agent in infections caused by a variety of gram-positive microorganisms. Because of significant nephrotoxicity the systemic use of bacitracin was subsequently limited to penicillin-resistant staphylococcal infections, and the drug was widely used topically. The recent advent of penicillinase-resistant penicillins may be expected to further reduce the systemic use of bacitracin in the future.

Commercial bacitracin with a potency of about 50 units per milligram is a neutral water-soluble substance consisting of a mixture of

peptides with molecular weights near 1450.[1] It is stable in the dry state for many months, and in neutral solution for more than one week at refrigerator temperature. Sterile bacitracin is supplied in vials containing 10,000 or 50,000 units. Solutions for intramuscular injection are prepared in sterile saline to contain 5000 to 10,000 units per milliliter; those for topical instillations should contain 500 to 1000 units per milliliter.

ANTIMICROBIAL ACTIVITY

Bacitracin is bactericidal for many gram-positive microorganisms in concentrations of 0.01 to 2.0 units per milliliter. The drug is largely inactive against gram-negative bacteria. Resistant organisms are infrequently encountered in susceptible species, and resistance does not emerge rapidly in clinical infections. There is no significant cross-resistance with other antimicrobial drugs.

Because of its selective activity against gram-positive organisms bacitracin is usually combined in topical preparations with polymyxin or neomycin, which are active against gram-negative bacteria. Large numbers of such mixtures for topical use are on the market.

Occasionally bacitracin enters into synergistic combinations with other drugs, particularly penicillin, in its action against enterococci or staphylococci. This combined effect has been used to advantage in certain patients suffering from particularly resistant infections.

TOXICITY

The principal undesirable effect of bacitracin is its nephrotoxicity, which limits severely the dose and time of its administration. Almost as soon as systemic levels of the drug are reached after intramuscular injection, there is proteinuria, hematuria and cylindruria of varying severity. Although these testify to the irritating effect on glomeruli and tubules, they are in themselves no evidence of significant damage, and they disappear promptly after the drug has been discontinued. Even during continuing bacitracin therapy the peak of hematuria and proteinuria is reached in about a week, and subsequently their intensity tends to decline. Proteinuria and hematuria are not considered a reason for discontinuing administration of bacitracin. Nevetheless, significant nitrogen retention, which may appear abruptly or gradually, is an important warning which must be heeded. Frequent laboratory tests for nitrogen retention are therefore mandatory in systemic administration of bacitracin. This is particularly important in patients with poor kidney function, in whom the drug may cumulate rapidly and may lead to uremia, unless the dose is suitably reduced.

ABSORPTION, DISTRIBUTION AND EXCRETION

After oral administration or topical application to skin, absorption of bacitracin is so limited that significant blood or tissue concentrations are not achieved. Similarly, absorption is small after instillation of bacitracin into joint or pleural spaces, and consequently systemic toxicity is usually minimal or absent. After intramuscular injection (the intravenous route is not accepted) absorption is rapid and complete, producing blood and tissue levels of 0.2 to 2.0 units per milliliter of serum with doses of 200 to 300 units of bacitracin per kilogram of body weight injected every 6 hours. Intramuscularly injected bacitracin does not readily reach the central nervous system. Orally administered bacitracin is excreted in the feces. Parenterally injected bacitracin is excreted mainly by way of the urine.

ADMINISTRATION AND DOSAGE

Intramuscular Injection. Bacitracin is available as sterile powder packaged in amounts of 10,000 and 50,000 units per vial. The material is dissolved in enough sterile physiologic salt solution containing 2 per cent procaine hydrochloride to give a concentration of 5000 to 10,000 units per milliliter. The total daily dose for adults is 60,000 to 100,000 units, and for children 200 to 400 units per kilogram. The total daily dose is given in three to four evenly spaced injections. During parenteral bacitracin therapy an adequate fluid intake must be maintained to result in an ample urine volume. Proteinuria and hematuria occur regularly and are not considered a reason for discontinuing therapy. Significant nitrogen retention is an important danger signal, however. Laboratory tests for nitrogen retention must therefore be carried out every two to four days. Extreme caution is necessary when administering intramuscular bacitracin to patients with pre-existing renal damage.

Topical Application. Bacitracin enjoys great popularity in topical therapy, in ointments, solutions, sprays, troches, and so on. Commonly, bacitracin is combined in such preparations with other drugs which act on gram-negative bacteria. These topical preparations are useful in pyogenic dermatoses and superficial mixed bacterial infections.

Bacitracin solutions can be instilled into pleural cavity, joint space, infected surgical wounds, radically débrided osteomyelitis and other situations in which the rapid bactericidal effect of the drug in direct contact with infecting staphylococci provides a useful addition to systemic therapy with other agents. The concentration of bacitracin in such solutions is usually 1000 units per milliliter, and the total daily dose does not exceed 100,000 units.

CLINICAL USE

Bacitracin has no place in the treatment of a large majority of clinical infections, even those caused by bacitracin-susceptible gram-positive organisms. It finds its wide application in topical therapy of superficial infections of skin, mucous membranes, eye, ear, and so on, in which it often acts similarly to a surface disinfectant rather than as an antimicrobial substance active in tissue. Until the recent penicillinase-resistant penicillins it was an essential constituent of specifically selected drug combinations for the treatment of drug-resistant staphylococcal sepsis, pneumonia, osteomyelitis, endocarditis and similar life-threatening illness.[10] In selected cases it may still occupy a useful position in such desperately ill patients. Nevertheless its systemic toxicity suggests that it be used principally for instillations in surgical infections and empyema caused by staphylococci.

In acute staphylococcal pneumonia of infants and children early drainage of the pleural space is now widely recommended. In addition to such drainage by a closed system, the intermittent instillation of bacitracin solutions (2000 to 10,000 units) may contribute to the rapid sterilization of the area, and the prevention of empyema. Similarly, we have found it useful to instill bacitracin solutions into areas of staphylococcal osteomyelitis which have been radically débrided, provided laboratory tests indicated susceptibility of the infecting staphylococcus to bacitracin alone, or in combination with other drugs.[10]

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VANCOMYCIN AND RISTOCETIN

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Although the problem of staphylococcal infections is not a new one, in recent years it has become of increasing concern. In addition to the dramatic epidemics of staphylococcal disease which have occurred in newborn nurseries, some of the most important aspects of this problem relate to diseases occurring principally in infants and children. Although the occurrence of certain clinical types of staphylococcal disease, such as osteomyelitis, has decreased, others, e.g. staphylococcal pneumonia and empyema in infancy, have shown an apparent striking increase. The historical aspects, the fundamental biologic nature of the organism, alterations in host response, the influence of antimicrobial drugs and other factors have been reviewed.[30, 37, 39, 40, 44] Finland[55] has detailed the circumstances contributing to the increased significance of staphylococcal infections in recent years. Whereas the use of antibiotics in many other infections, such as those caused by pneumococci and hemolytic streptococci, had continued to be effective, antimicrobial therapy of staphylococcal infections, though at first encouraging, was becoming disappointing. One of the main reasons for this was that staphylococci involved in most hospital-acquired infections had shown a pattern of increasing resistance to the generally available antimicrobial agents.[30, 37, 39, 40, 44, 55] Because of these factors, considerable effort has been directed to the development of newer antimicrobial agents against staphylococcal infections. Vancomycin and ristocetin are two of the newer such agents which have become available.

VANCOMYCIN

CHEMICAL AND PHYSICAL PROPERTIES

Vancomycin* is produced by *Streptomyces orientalis*. The first culture

* The trade name of Eli Lilly and Company for vancomycin is Vancocin.

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was obtained from a soil sample obtained by a missionary in the Indonesian jungles. Vancomycin hydrochloride, which appears to have no significant chemical relation to any other known antibiotic, is a white solid material, and is a large molecule, having a molecular weight of approximately 3300. The ultimate composition and microbial activities of vancomycin are not entirely known at present, since electrophoretic studies have shown that the crystalline substance contains some 20 per cent of a second component, the biological activity of which has not been determined.[21, 33, 34, 57]

ANTIMICROBIAL PROPERTIES

In addition to staphylococci, other organisms usually susceptible to vancomycin include hemolytic streptococci, pneumococci, enterococci, gonococci, cornyebacteria and clostridia. It is not effective against Klebsiella, Brucella, Proteus, Shigella, Salmonella, Pseudomonas, Aerobacter and other coliform organisms, nor *Mycobacterium tuberculosis*, fungi and yeast[25] (personal communication from R. S. Griffith). Extensive studies by many investigators have shown that pathogenic staphylococci are almost uniformly susceptible to vancomycin in low concentrations (less than 3 micrograms per milliliter). Of the many strains so far studied, only 5 have shown growth in concentrations greater than 10 micrograms per milliliter.[11, 14–16, 25, 26, 43, 56]

Vancomycin is bactericidal against multiplying bacteria in a manner similar to penicillin.[57] Bactericidal and bacteriostatic levels are similar, and the action of vancomycin is not greatly affected by the presence of serum.[26, 36] Wise[56] and Kirby and Divelbiss[26] have reported vancomycin to have greater activity in vitro than ristocetin and kanamycin. Garrod and Waterworth[11] concluded that vancomycin has greater bactericidal activity than seven other antistaphylococcal antibiotics which were studied.

Vancomycin does not exhibit cross-resistance with other known antibiotics. Several workers have noted that resistance in vitro of staphylococci to vancomycin rarely develops and then only very slowly and of a small degree even after as many as 28 daily subcultures.[14–16, 36] Garrod and Waterworth[11] feel that resistance to vancomycin of a degree to obviate the therapeutic effect apparently cannot develop in staphylococci.

In our laboratory we have not observed staphylococci resistant to vancomycin, nor has resistance developed during rather prolonged treatment of patients with vancomycin. Other workers[14, 26] have confirmed that staphylococci retain their susceptibility to vancomycin after two to four weeks of vancomycin therapy.

ABSORPTION, DISTRIBUTION AND EXCRETION

Lee[31, 32] reported on the absorption, distribution and excretion in dogs and other animals.

Bactericidal serum concentrations in human beings are readily achieved and maintained by intravenous administration. In 16 children receiving vancomycin in a dose of 20 mg. per kilogram as a single intravenous injection, a peak serum value of 52 micrograms per milliliter was promptly reached at one hour, the concentration slowly falling to a range of 1.6 to 13 micrograms 12 hours after administration.[51] No difference was found in the average values in five patients under the age of two weeks as compared to the older children. In 14 patients receiving 13.3 mg. per kilogram of vancomycin by intramuscular injection the peak concentration occurred 4 hours after administration and averaged approximately 10 micrograms per milliliter. Therapeutic concentrations were maintained for at least eight hours after injection.[51]

Kirby and Divelbiss[26] and Geraci et al.[14] reported on serum concentrations in adults following intravenous administration and concluded that 1 gm. every 12 hours was usually the most desirable regimen in this age group.

Vancomycin is excreted chiefly through the kidneys, more than 80 per cent of the administered dose within a 24-hour period being recovered from the urine. Considerably higher serum concentrations occur and may persist for long periods in patients with impaired renal function.[26] The half-life of vancomycin in the blood has been estimated to be approximately six hours.[15]

Vancomycin diffuses readily into the pleural, ascitic and synovial fluids, but only small amounts are secreted in the bile. It does not diffuse into the spinal fluid through normal meninges even after multiple doses, but may pass the blood-brain barrier in some instances when the meninges are inflamed.[25]

ADMINISTRATION AND DOSAGE FORM

Vancomycin is available as 0.5 gm. of vancomycin hydrochloride in 10-ml. rubber-stoppered ampules. At the time of use, 10 ml. of water for injection, U.S.P., is added to the ampule.

At present the drug should be administered only by the intravenous route. An intramuscular preparation has also been utilized in experimental studies (unpublished observations), but this product is not commercially available.* Spears and Koch[51] have administered vancomycin intramuscularly after mixing with hydrocortisone to reduce the pain associated with injection. There are several methods of intravenous administration: (*a*) Intermittent infusion: the desired amount of the drug can be added to 50 to 150 ml. of normal saline or 5 per cent glucose in water and this infusion given rapidly over a period of 20 to 30 minutes at 8- to 12-hour intervals until the total calculated daily dose is administered. (*b*) Direct injection: one third to one

* Personal communication from R. S. Griffith, M.D.

fourth of the total daily dose mixed with 10 ml. of water for injection can be injected directly into a large vein or into the infusion tubing. This injection should be given slowly over at least a five-minute period and can be repeated at 6- to 8-hour intervals until the total daily dose has been administered. (*c*) Continuous injection: the total daily dose can be added to an appropriate amount of normal saline or 5 per cent glucose (in a ratio of 1 gm. of vancomycin to 1000 ml. of fluid) and the rate of administration of the intravenous infusion adjusted so that the patient receives the total calculated daily dose over a 24-hour period. Continuous intravenous administration may be achieved by means of a venous cutdown or through femoral or caval catheters.

If the patient is receiving a continuous infusion of fluids with which vancomycin is not compatible, the infusion bottles can be changed temporarily. All the foregoing methods have been utilized in this Clinic. Methods (*a*) and (*b*) have the advantage of allowing a large dose to be given immediately and at frequent intervals in patients with overwhelming infections. The incidence of phlebitis seems to be more frequent with direct injection than with other methods. Although intermittent infusion is probably the easiest method, we feel that the method of administration should be individualized.

In children a total daily dose of 20 mg. per pound of body weight per day divided into equal aliquots and administered intermittently at 8- or 12-hour intervals or given by continuous drip as described above is usually satisfactory. In serious, overwhelming infection we have used doses as high as 68 mg. initially without significant untoward effects. For premature and full-term newborn infants a dose of 6 mg. per pound per day has proved satisfactory and safe,[2] though others[38] have recommended a dose of 15 mg. Until more experience has been accumulated, it is probably desirable to use the drug in this age group with caution and to adjust dosage on the basis of serial determinations of serum concentration.

The usual adult dose is 2 gm. daily, and doses larger than this should be avoided except occasionally for initiating therapy in a severely ill patient with normal renal function. Vancomycin should be used cautiously in patients with reduced renal function, the dosage being titrated according to serum levels. The oral administration of vancomycin has been used in the management of enterocolitis caused by penicillin-resistant staphylococci and also in conjunction with systemic therapy in some patients.[21, 26, 34]

TOXICITY AND SIDE EFFECTS

Vancomycin has a low order of toxicity in experimental mice, rats and other animals. In monkeys and dogs, daily intravenous dosage of 25 to 50 mg. per kilogram for 3 months or longer produced no signs of toxicity.[2]

Further purification of the antibiotic has reduced the incidence of chemical phlebitis, and pain at the site of intravenous injection, which was a common occurrence with the initial lots of vancomycin available for clinical investigation, so that with the relatively pure material which has been available more recently untoward effects of these types have presented little difficulty. Phlebitis can be minimized by using dilute solutions and alternating the sites of injection. Rapid intravenous injection of vancomycin may cause a feeling of warmth, generalized tingling and nausea, but this may be avoided by slowing the rate of injection and usually does not occur when the dose is given over a period of 20 to 30 minutes.

On occasion, chills, fever, slight renal irritation, urticaria and macular rashes have occurred during or after the administration of vancomycin in some patients, as is true with other compounds of high molecular weight. Such reactions have sometimes occurred in a nonpredictable fashion, beginning with the first dose of vancomycin; in other patients, vancomycin was tolerated without reaction several months later. The febrile reaction occurring with some of the earlier lots often made clinical evaluation of therapeutic response difficult.[43] If these reactions are severe, the drug should be discontinued. These manifestations may be minimized by the concurrent administration of antihistamine or hydrocortisone.[13, 27, 51] Although these untoward effects were common with early lots, they are much less frequent with the more purified material. Three instances of possible cross-sensitization between vancomycin and other antibiotics such as streptomycin have been reported.[7] Though this is extremely rare, precaution should be observed against anaphylaxis.[49, 51]

Hearing loss has been reported in a few patients when excessively high serum levels—levels 5 to 10 greater than the necessary therapeutic concentration—were present.[13, 25] In certain patients the deafness has been temporary and reversible when therapy was discontinued.[43] Because of these observations vancomycin should be used cautiously in patients with reduced renal function, and when long-term administration is planned, tests of auditory acuity along with serial measurements of renal function should be performed before starting therapy and at frequent intervals during and after the course of therapy.

Hematopoietic disturbances have not been a problem with the use of vancomycin, only two cases of transient leukopenia having been observed.[3] Hepatic toxicity has not been reported. Nevertheless, as with the prolonged intravenous administration of any drug, it is suggested that appropriate hematologic studies, urinalysis and liver and renal function tests be performed periodically, especially if the medication is to be used in a dosage larger than 20 mg. per pound per day in a child or more than 2 gm. per day in adults over a period longer than 2 weeks.

INDICATIONS AND CLINICAL USE

The principal clinical indication for the use of vancomycin lies in the treatment of severe infections due to pathogenic staphylococci. Vancomycin is not indicated for treatment of comparatively mild staphylococcal infections, but may be the drug of choice when patients have failed to respond to the commonly used antimicrobial agents or when the causative strain is resistant to other antibiotics. It may be used in patients seriously ill with infections caused by other gram-positive organisms;[28] however, infections due to streptococci and pneumococci usually respond well to more easily administered agents such as penicillin, and its use in such infection will not be reviewed here.

A significant experience with the use of vancomycin in serious staphylococcal infections has now accumulated.

Staphylococcal Pneumonia and Empyema. In 1959 Riley and Ryan[43] reported that 5 infants and children critically ill with staphylococcal pneumonia responded satisfactorily to vancomycin. Since this report a much larger experience with the use of vancomycin has been accumulated in this Clinic. The initial impression of excellent results in serious staphylococcal pneumonia, many cases of which had been unsuccessfully previously treated with other antibiotics, has been confirmed. Spears and Koch[51] also reported good results in several children with staphylococcal pneumonia. Kirby et al.[28] and Ehrenkranz[7] found vancomycin effective in several cases of staphylococcal pneumonia in adults in many of whom previous antibiotic therapy had failed.

The role of vancomycin therapy in treatment of staphylococcal empyema is unsettled. Geraci et al.[14] could not demonstrate any concentration of the drug in empyema fluid after four doses. Spears and Koch[51] feel that vancomycin should be used in conjunction with another antibiotic in situations in which the antibiotic must cross tissue barriers, as in meningitis and empyema pockets. On the other hand, Ehrenkranz[7] has reported success with vancomycin in staphylococcal empyema after catheter drainage and therapy with other drugs had apparently failed. Our experience with vancomycin in staphylococcal empyema has been satisfactory.

Staphylococcal Infections of Skin and Soft Tissues. In several infants and children with severe, life-threatening soft tissue infections treated with vancomycin in this Clinic, the results have been good.[42, 43] Other workers have observed a satisfactory response to vancomycin in patients with cellulitis, recurrent furunculosis, carbuncles and deep postoperative wound infections, the latter due for the most part to antibiotic-resistant staphylococci.[14, 25, 26, 28] The role of surgical drainage as an adjunct to therapy should not be neglected. Here vancomycin, because of difficulties in administration, should be reserved for patients in whom there has been a failure to respond to other antibiotics, those

with lesions caused by antibiotic-resistant organisms or those with lesions that are potentially life-threatening, such as cellulitis about the face and deep-seated wound infections, especially if there is a possibility of hematogenous dissemination.

Septicemia and Endocarditis. Promising results in the treatment of these conditions with vancomycin have been reported by several investigators. Many of the reported patients had serious, usually fatal underlying diseases complicated by septicemia due to antibiotic-resistant staphylococci. Riley and Ryan[43] reported a satisfactory response in eight of nine children with staphylococcal septicemia treated with vancomycin; since that report several additional patients have been treated successfully.[42] Three of four children with staphylococcal septicemia treated with vancomycin by Spears and Koch[51] were cured. Kirby and co-workers[27] have recently reported the treatment with vancomycin of 33 adults with staphylococcal septicemia. Of these, most of whom were in the older age groups and had serious underlying illnesses, 20 were cured, a number of whom had failed to improve with other antibiotics to which the causative organism was susceptible, 6 were improved, but died of underlying diseases, and 7 were classified as treatment failures, although most of these last had overwhelming infections and died shortly after therapy was initiated. Blood cultures may remain positive for three to four days after initiation of vancomycin therapy in some patients who obtain a satisfactory response.[25] A 10-year-old boy with staphylococcal septicemia and septic arthritis who also had renal failure due to pyelonephritis exhibited dramatic improvement and a prompt bacteriologic response with no worsening of his renal status after treatment with vancomycin.[54] Dosage was governed by the results of serial determinations of the serum levels of vancomycin.

Of four children with staphylococcal endocarditis treated with vancomycin, Spears and Koch[51] considered one cured, one improved, and one unimproved; one with uremia died of his infection after four days of therapy. The infection was promptly eradicated in two children with staphylococcal endocarditis treated with vancomycin by Riley and Ryan.[43] Geraci et al.[13] reported the successful treatment of four of six adults with acute staphylococcal endocarditis with vancomycin, no patients with this type of acute endocarditis having been cured previously in his clinic. Of the two remaining patients, the infection was not controlled by vancomycin in one, and the other died two weeks after therapy was terminated of his primary disease, the infection having been eradicated. Since the four successfully treated patients received vancomycin for 28, 20, 18 and 28 days respectively, and the results of the serum bactericidal tests were satisfactory, these workers suggested that short-term (2 weeks) treatment with vancomycin alone might be satisfactory in staphylococcal endocarditis.

Osteomyelitis. We have treated a small number of patients with staphylococcal osteomyelitis with vancomycin with good results.[42, 43] Other workers[7, 14, 26, 28] have also reported satisfactory results in several patients with osteomyelitis and septic arthritis.

Staphylococcal Enterocolitis. Because of the high concentration in the stools after oral administration, it has been speculated that vancomycin administered orally might be useful in the treatment of staphylococcal enterocolitis.[14]

In our hands a satisfactory treatment regimen in patients with severe staphylococcal disease requiring long-term therapy, such as staphylococcal pneumonia, has been to use vancomycin during the initial period, for perhaps 7 to 10 days, and then complete the course of treatment with a more easily administered antistaphylococcal agent or agents.

Waisbren et al.[53] concluded that vancomycin did not show any clinical superiority over ristocetin and kanamycin in their experience with the treatment of staphylococcal infections. In a panel discussion on the use of various antibiotics in staphylococcal infections there was general agreement that vancomycin and ristocetin were two of the most effective antistaphylococcal agents, the majority of the panelists regarding vancomycin as the more potent of the two.[9]

RISTOCETIN

Ristocetin* was first isolated by Grundy and co-workers[18] from cultures of *Nocardia lurida*, an actinomycete, which was first recovered from a soil sample from the Garden of the Gods, Colorado Springs, Colorado. To date, no other culture which produces ristocetin has been found.

CHEMICAL AND PHYSICAL PROPERTIES

Two related substances, ristocetins A and B, which are large molecules, have been isolated. Although the chemical characteristics are not completely defined, ristocetin B is 3 to 4 times as active as ristocetin A, which has an arbitrarily assigned potency of 1000 units per milligram.[19] Body fluids containing ristocetin may be stored at 10° C. for at least 5 days without deterioration.[47]

ANTIMICROBIAL PROPERTIES

Ristocetin has activity against gram-positive bacteria, including staphylococci, pneumococci, streptococci and mycobacteria, but is not active against gram-negative bacteria, including *Hemophilus influenzae* and Neisseria species as well as yeast and a few protozoa which have been studied. Although most strains of *Staphylococcus aureus*, including

* The trade name of Abbott Laboratories for ristocetin is Spontin.

many which are resistant to many other antimicrobial agents, are susceptible to ristocetin, some strains require a concentration somewhat higher than the minimum inhibitory concentration for a bactericidal effect.[1] Grundy and co-workers[18] and Romansky et al.[48] outlined in detail the antimicrobial spectrum in vitro of ristocetin. Cross-resistance among ristocetin, vancomycin, kanamycin and other antibiotics reportedly does not occur.[48, 50]

Early studies revealed a narrow range between bacteriostatic and bactericidal effects against streptococci, pneumococci and staphylococci, but with the accumulation of additional laboratory data, some strains have shown a greater variability in this range.[12, 17, 47, 50] The bactericidal activity of ristocetin is apparently not restricted to actively dividing cells.[17] Several workers have reported that ristocetin has less activity in vitro than vancomycin.[28, 50, 56] Wise[56] found that vancomycin was bactericidal against 12 of 13 strains of staphylococci, whereas ristocetin exhibited bactericidal action against only one of the thirteen.

Grundy and co-workers[17] reported that none of more than 400 cultures of streptococci, pneumococci and staphylococci were naturally resistant to ristocetin and that bacteria do not readily acquire resistance in vitro to the drug. Romansky, Limson and Hawkins[48] observed no development of resistance in 2 strains of *Staphylococcus aureus* isolated from purulent exudates after 45 subcultures. These workers reported that all of 35 strains of hemolytic *Staphylococcus aureus* were susceptible to less than 5 micrograms per milliliter of ristocetin, all of 74 strains of pneumococci were susceptible to 3 micrograms or less, and more than 70 per cent of 90 strains of streptococci were susceptible to 5 micrograms. Hsie et al.[22] reported that staphylococci slowly developed a low order of resistance to ristocetin as measured by the agar gradient technique.

The bactericidal properties of ristocetin have been emphasized by the manufacturers, and some investigators have referred to its bactericidal characteristics. Other workers, however,[35, 50] have reported it to be primarily bacteriostatic for staphylococci. Rantz[35] found that the bactericidal concentration of ristocetin for 42 strains of *Staphylococcus aureus* was threefold to more than tenfold greater than the 24-hour inhibitory concentration and was often 2 to 4 times, or more, greater than the 48-hour inhibitory concentration.

ABSORPTION, DISTRIBUTION AND EXCRETION

Hwang et al.[23] studied the pharmacologic properties and toxicity of ristocetin in animals. Dries, Asay and Koch[6] and Dries and Koch[4] studied both the intravenous and intramuscular administration of ristocetin in children ranging in age from 2 days to 15 years. Two hours

after a dose of 12.5 mg. per kilogram was administered rapidly intravenously in 8 children, serum levels varied from 1.3 to 10.6 micrograms per milliliter. Thereafter the level declined gradually to less than 0.7 microgram at 12 hours. After the intravenous administration of 25 mg. per kilogram in 13 children, the ristocetin content of the serum averaged approximately 18 micrograms per milliliter for 4 hours after injection and then gradually decreased to an average of 2.5 micrograms per milliliter at 12 hours. In 6 children receiving 50 mg. per kilogram per day as a 24-hour continuous intravenous infusion, the serum content ranged between 2.6 and 21.1 micrograms per milliliter during the infusion. When the drug was administered intramuscularly to 14 children in a dosage of 12.5 mg. per kilogram with hydrocortisone added in a ratio of 1 mg. to each 100 mg. of antibiotic, serum concentrations at 2 hours averaged 5.3 micrograms per milliliter and decreased to less than 0.7 microgram 12 hours after administration. Satisfactory serum levels, comparable to those obtained with intravenous administration, were obtained in 8 children who received 25 mg. per kilogram per day intramuscularly. Romansky and Olson[47] have reported on serum concentrations in adults. Intramuscular administration of ristocetin in doses of 200 to 500 mg. in adults was painful, and blood levels obtained by this route of administration were generally less than 5 micrograms per milliliter.[48]

Ristocetin diffuses freely into pleural and ascitic fluid; levels at 2 to 4 hours approximate those in the blood when 1 to 2 gm. is administered rapidly intravenously.[47]

Ristocetin does not readily pass the blood-brain barrier. In one pediatric patient with meningitis and 12 without meningitis, the spinal fluid content of ristocetin remained less than 0.7 microgram per milliliter, regardless of route of administration or dosage.[4] Spinal fluid concentrations in another study were less than 0.625 microgram per milliliter 3 hours after a 1-gm. dose despite concentrations in the blood at the same time between 5 and 20 micrograms per milliliter.[45, 48]

Excretion studies revealed that 40 to 50 per cent of a 1- to 2-gm. dose is recoverable in the urine in 24 hours.[47] Further studies are needed to ascertain whether transplacental diffusion occurs and whether the drug passes into bile, milk or seminal fluid. Oral ristocetin in doses of 2 to 4 gm. does not reduce the total bacterial count in the stools, but does reduce the number of enterococci and staphylococci. Ristocetin solutions containing 1 mg. per milliliter of antibiotic are apparently well tolerated by the tracheobronchial tree when used for nebulization therapy.[47]

DOSAGE AND ROUTES OF ADMINISTRATION

Ristocetin is available as a sterile, lyophilized powder in vials containing a mixture of ristocetins A and B, representing 500 mg. of ristocetin

A activity. Sterile solutions of ristocetin may be stored under refrigeration for one month without significant loss of potency.

Most investigators recommend a dose of 25 to 50 mg. per kilogram per day, depending on the type of infecting organism and severity of the disease, in both children and adults. Dries and Koch[5] recommend a dose of 50 mg. per kilogram per day intravenously or intramuscularly in children. A maximum dosage of 25 mg. per kilogram per day is usually adequate in pneumococcal and streptococcal infections. The majority of staphylococcal infections are controlled by 25 to 50 mg. per kilogram per day, but in severe infections, including bacterial endocarditis, a larger dose is often desirable during the early stages of the disease. Larger dosages should be reduced to 25 mg. per kilogram per day after clinical response. Since ristocetin is excreted by the kidney, dosage should be considerably reduced (to approximately half) in patients with renal impairment, to prevent excessive serum accumulation. A dose of 15 mg. per kilogram per day has been recommended for premature and newborn infants.[38]

Ristocetin should be administered by the intravenous route. A 0.5 to 1 per cent solution should be prepared, using approximately 100 ml. of 5 per cent glucose or normal or hypotonic saline. Solutions should be prepared so that the maximum concentration of antibiotic does not exceed 25 mg. per milliliter. The solution may be given by the drip technique over 35 to 40 minutes, or may be injected directly into the tubing of an intravenous infusion used for fluid therapy or into a large vein, making certain that the time of administration is at least 5 minutes.

Generally, the total daily dose is divided into 2 portions and administered at 12-hour intervals. In more severe infections, particularly those caused by the Staphylococcus, an eight-hour schedule may be used. When doses of 50 mg. per kilogram per day or more are used, the total daily dose should be divided into 3 equal parts. The duration of therapy must be determined by the kind of infection and the clinical course of the disease.

Dries and Koch[5] report that the intravenous preparation of ristocetin can be safely administered intramuscularly by adding 1 mg. of hydrocortisone to each 100 mg. of antibiotic to decrease the inflammatory response at the site of injection.

TOXICITY AND SIDE EFFECTS

Side effects associated with the use of ristocetin are not uncommon, having been noted in 29, or 20.8 per cent, of one series of 139 patients[47] and in 29 per cent of another series of 76 patients in the pediatric age group.[5] In certain of the cases toxic effects could not be attributed solely to ristocetin, since the patients had received other potentially

toxic drugs also. One of the more serious and unfortunately more common untoward effect is that affecting the hematopoietic system. Romansky and Olson[47] reported that varying degrees of leukopenia, neutropenia, thrombocytopenia and eosinophilia, either alone or in combination, occurred in 12.9 per cent of a series of 139 patients treated with ristocetin. Leukopenia or neutropenia occurred in six, and eosinophilia, which may presage the development of neutropenia or leukopenia, in 10 of 76 pediatric patients.[5] Thrombocytopenia, although less common than neutropenia, may occur even with currently recommended therapeutic regimens.[10] Bone marrow examination and other studies suggest that ristocetin exerts its effect on the circulatory blood elements rather than on the bone marrow.[10, 47] To date, the side effects appear reversible on reduction of dosage or discontinuance of the drug, and all reported patients have recovered from the various degrees of leukopenia and thrombocytopenia. It is recommended that a complete hemogram, including hemoglobin determination, leukocyte, differential and platelet counts, be done on alternate days in children receiving more than 25 mg. per kilogram per day or in adults receiving more than 2 gm. a day and twice a week in patients receiving lower dosages. In general, the drug should be withdrawn if the total white cell count falls below 5000 cells per cubic millimeter or if the neutrophile count falls to less than 50 per cent of the total leukocytes even if the total white cell count exceeds 5000 cells per cubic millimeter.

Phlebitis due to chemical irritation of the vein may occur at the site of injection, but can usually be controlled by reducing the volume of antibiotic solution.

Drug fever, and a maculopapular rash associated with ristocetin administration, as well as instances of deafness and nephrotoxicity possibly related to ristocetin, have been reported.[47, 53]

It seems clear that the occurrence of toxicity is directly related to the size of dose of ristocetin, the incidence rising steeply when the recommended daily dose is exceeded. A similar relation between the total dosage of ristocetin administered and the incidence of side effects can be demonstrated. In a review of 333 cases the incidence of side effects rose in a stepwise fashion from 9.4 per cent with a maximum daily dose of between 1 and 1.9 gm. to 41 per cent with a daily dose of 4 to 4.9 gm.[20] With improved methods of manufacture and a more purified material, there has been a decline in the incidence of side effects, including those affecting the hematopoietic system.

INDICATIONS AND CLINICAL USE

Although ristocetin may be effective in the treatment of streptococcal, pneumococcal and other infections due to gram-positive bacteria, it has found its greatest use in the management of staphylococcal and enterococcal infections. Six cases of pneumococcal pneumonia treated with

ristocetin exhibited a rapid defervescence.[48] Romansky and Holmes[46] have reported the successful short-term (13 to 24 days) treatment of 6 patients with enterococcal endocarditis. Since that time other reports of the successful treatment of enterococcal endocarditis with ristocetin have appeared.

The largest reported experience in the use of ristocetin in infancy and childhood has come from the group at the Los Angeles Childrens Hospital.[4, 5, 6] Seventy-six hospitalized infants and children, 27 of whom were considered severely ill, were treated for pyogenic infections with ristocetin administered both intravenously and intramuscularly. Forty-seven had infections due to coagulase-positive staphylococci, of which 19 were resistant to penicillin and 16 to tetracycline, and the majority of the remainder pneumococcal, hemolytic streptococcal and enterococcal infections. As shown in Table 13, of the 76 patients, 87 per cent were considered improved after treatment with ristocetin. Twenty-seven of the children with severe staphylococcal infections received other drugs in addition to ristocetin. All of 5 patients with staphylococcal septicemia and 11 of 13 patients with staphylococcal pneumonia and empyema were considered cured. Of four patients with staphylococcal endocarditis, two were cured and two were unimproved. There was no improvement in two children with staphylococcal meningitis. Of the 19 patients with staphylococcal infections resistant to penicillin, 6 failed to respond to ristocetin, including 2 with bacterial endocarditis, 2 with meningitis and 2 with pneumonia and empyema.

The data of these workers suggest a relation between dosage and

TABLE 13. *Clinical Effectiveness of Ristocetin in 76 Patients*

DIAGNOSIS	NUMBER	ORGANISM	CLINICAL RESULTS		
			Cured	Unimproved	Died
Septicemia	5	Staphylococcus*	5	—	—
Septicemia	1	Enterococcus	1	—	—
Acute bacterial pericarditis	1	Staphylococcus*	—	—	1
Subacute bacterial endocarditis	4	Staphylococcus*	2	2	—
Meningitis	2	Staphylococcus*	—	2	—
Cellulitis and/or abscess	12	Staphylococcus	12	—	—
Osteomyelitis	1	H. influenzae B*	1	—	—
Pneumonia and empyema	13	Staphylococcus*	11	2	—
Pneumonia and empyema	1	Pneumococcus	—	1	—
Bronchopneumonia	18	Various	18	—	—
Respiratory tract infections	15	Various	15	—	—
Enterocolitis	1	Staphylococcus	1	—	—
Bronchiectasis due to fibrocystic disease	1	Staphylococcus	—	—	1
Disseminated moniliasis	1	Candida and staphylococcus	—	1	—
Totals	76		66	8	2

From Dries et al.[5]

* Received additional antibiotics.

clinical result. Of the 35 patients treated with 25 mg. per kilogram per day, 8 failed to improve, and one death occurred in this group. Only 4 of 38 patients treated with 50 mg. per kilogram per day failed to respond. Of 5 patients treated with 75 mg. per kilogram per day, 4 were considered cured, and one, a child with fulminating staphylococcal bacteremia and pericarditis following cardiotomy, expired. Three of the 4 patients considered cured had not responded previously to 25 or 50 mg. per kilogram per day.

Of the total 76 patients, 29 per cent showed some sort of side effects to ristocetin; severe toxic reaction such as leukopenia and neutropenia occurred in 7.6 per cent of the patients. All subsided promptly, however, with discontinuance of the antibiotic.

Romansky and Olson[47] reviewed 139 cases of infections collected from the literature, mostly in adult patients, treated with ristocetin and considered 89 to have a clearly established staphylococcal etiology. The number and types of cases and these workers' interpretation of the results of therapy are shown in Table 14. Fifty-seven patients (63.9 per cent) were regarded as cured, and 19 (21.3 per cent) improved. There were 6 failures (6.7 per cent), and 7 (7.8 per cent) patients died of unrelated causes or before ristocetin therapy could be evaluated.

In 40 staphylococcal pulmonary infections, 33 of which had previously been treated with other antibiotics without apparent effect, ristocetin was considered to have a curative effect in 30, or 75 per cent. Romansky and Olson[47] consider that ristocetin can be used as the sole agent in the treatment of staphylococcal pulmonary infections.

Ristocetin was considered to have cured 13 of 19 patients with skin and soft tissue infections, including patients with widespread furunculosis and multiple abscesses.

Of the 11 patients with staphylococcal osteomyelitis and arthritis, 9 of whom had not responded to other antibiotics, 3 were considered cured, and the remaining 8 improved after the use of ristocetin in conjunction with surgery. An initial dose of 50 to 75 mg. per kilogram per day fol-

TABLE 14. *Ristocetin—Results of Therapy in Staphylococcal Infections*

	NUMBER	CURED	IMPROVED	FAILED	OTHER OUTCOME *
Pneumonia, lung abscess	40	30	2	2	6
Skin and soft tissues	19	13	6		
Osteomyelitis, arthritis	11	3	8		
Endocarditis	7	5		2	
Septicemia	8	3	2	2	1
Meningitis, brain abscess	2	2			
Visceral	2	1	1		
Totals	89	57	19	6	7

Modified from Romansky and Olson.[47]

* Died of unrelated causes or before therapy could be evaluated.

lowed by 25 to 50 mg. per kilogram per day is recommended by Terry and Bradley[52] in the treatment of osteomyelitis and suppurative arthritis in childhood.

Five of seven patients with staphylococcal endocarditis were considered cured with ristocetin therapy. All the patients had been treated with one or more antibiotics before ristocetin therapy was instituted and had positive blood cultures when ristocetin was begun. Four of the five successfully treated patients were adults and received 1.5 to 2 gm. every 8 hours for 12 to 18 days. Dries and co-workers[6] successfully treated an 11-year-old girl with 75 mg. per kilogram per day for 35 days after 25 mg. per kilogram per day had failed to produce improvement.

Ristocetin was considered curative in three of eight patients with septicemia and is credited with producing improvement in two additional patients. Rantz and Jawetz[35] reported failures with ristocetin in three cases of sepsis with bacteremia due to *Staphylococcus aureus*. Bacteremia persisted in each patient during therapy, and there was no clinical improvement. Romansky and Olson[47] are of the opinion that these failures may well be related to insufficient dose of the drug and the fact that it was given by constant intravenous drip, precluding the attainment of peak concentrations. A patient with staphylococcal septicemia while under treatment with adrenal steroids, reported by Knight,[29] did not respond to 6 gm. per day.

Two patients with staphylococcal meningitis obtained a good result with ristocetin therapy.[12, 24] Of particular interest is the fact that studies of the spinal fluid in one of the cases[24] revealed that ristocetin had crossed the blood-brain barrier.

Herting and co-workers[20] of Abbott Laboratories surveyed 333 cases treated with ristocetin, including those published in the literature as well as reports submitted directly by clinicians to the manufacturer. On the basis of "an analysis conducted entirely by machine methods to minimize personal factors in the evaluation," 60 per cent of the patients treated were considered cured and a further 17 per cent "improved," while 23 per cent demonstrated no response.

Waisbren and co-workers[53] administered ristocetin, vancomycin and kanamycin alternately to 131 patients with severe staphylococcal infections or bacterial endocarditis. They concluded that no one of the three antibiotics showed clinical superiority over the others. Although significant ototoxicity and nephrotoxicity were found with all three, ristocetin, in addition, caused a high incidence of skin reactions and depression of the granulocytic series of the white blood cells in some patients.

SUMMARY

Vancomycin, a bactericidal antibiotic, is a valuable drug for the treatment of staphylococcal infections. Because it must be administered

intravenously, it should be used chiefly for severe infections unlikely to respond to other antibiotics. Staphylococci resistant to vancomycin have not been encountered, and effective serum concentrations are readily obtained. With further purification of the drug, side effects have been much less common. The antibiotic should be used cautiously in the presence of renal insufficiency, since excessive serum concentrations may produce deafness.

Ristocetin is an effective agent in the management of staphylococcal infections. Because of difficulties in administration and untoward reactions, it should be reserved for severe infections not expected to be improved by more conventional antimicrobials. Its action is apparently not consistently bactericidal. Side effects, the most serious of which is hematopoietic depression, are not infrequent, but are usually reversible and can be reduced by adherence to recommended dosage schedules. Preliminary data suggest that it may be used effectively in the short-term therapy of enterococcal endocarditis.

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SULFONAMIDES

Shifting Status in Pediatrics

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In 1935 Domagk[2] described experimental and clinical observations on the activity of Prontosil against streptococcal and pneumococcal infections. These observations signalled the advent of chemotherapy with sulfonamide agents in bacterial infections in man. In the ensuing years almost 6000 sulfonamide compounds have been investigated for therapeutic usefulness, although only a few have been widely used in this country. It is beyond the scope of this paper extensively to review therapy with the sulfonamide agents. A brief consideration of presently available and commonly prescribed sulfonamide agents is presented along with consideration of the decreasing role of these drugs in the treatment of infections in children.

PHARMACODYNAMICS

For convenience the sulfonamide drugs can be considered to fall into three groups, depending upon their absorption after oral administration: (1) the rapidly absorbed and rapidly excreted agents, (2) the slowly excreted drugs, and (3) the "non-absorbed" compounds. Examples of some of these are listed in Table 15. No consideration will be given to those compounds which are available for parenteral use. Their antibacterial activities and other properties do not differ from those drugs administered by mouth.

Compounds in the first group are absorbed rapidly from the upper gastrointestinal tract, reach peak blood concentrations in one-half to

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TABLE 15. *Some Sulfonamide Agents in Common Use*

GENERIC TERM	COMMON TERM*
Rapidly Absorbed and Rapidly Excreted Sulfonamide Agents	
Sulfadiazine	Sulfadiazine
Sulfamerazine	Sulfamerazine
Sulfamethazine	Sulfamethazine
Sulfacetamide	Sulfacetamide
Sulfisoxazole	Gantrisin
Acetyl sulfisoxazole	Acetyl Gantrisin
Sulfadimetine; sulfisomidine	Elkosin
Sulfamethizole	Thiosulfil
Triple or quadruple mixtures	Many
Rapidly Absorbed and Slowly Excreted Sulfonamides	
Sulfaethylthiadiazole; sulfaethidole	Sul-Spansion; Sul-Spantab
Sulfadimethoxine	Madribon
Sulfamethoxypyridazine	Kynex; Midicel
"Nonabsorbed" Sulfonamides	
Succinylsulfathiazole	Sulfasuxidine
Phthalylsulfathiazole	Sulfathaladine
Sulfaguanidine	Sulfaguanidine
Phthalylsulfacetamide	Phthalylsulfacetamide
Paranitrosulfathiazole	Nisulfazole
Salicylazosulfapyridine	Azulfidine

* It is not possible to include all the trade names for these preparations.

two hours and are then excreted rather rapidly so that bacteriostatic levels usually do not persist in the blood for periods longer than six to eight hours. These agents are chiefly excreted by the kidney in free and conjugated forms, although lesser amounts are present in the feces, bile, breast milk and other secretions. Excretion by the kidney is accomplished chiefly by glomerular filtration, although tubular absorption or excretion may be of importance in certain compounds.

Drugs in the second group are rapidly absorbed from the upper part of the intestinal tract and reach peak blood levels in one-half to two hours. The blood levels drop slowly and can be maintained in effective bacteriostatic concentrations for periods of at least 12 to 24 hours after a single oral dose. For all these preparations, except sulfaethylthiadiazole, the prolonged presence of these agents in the blood is a reflection of their slow excretion by the kidney. Tubular reabsorption permits recirculation of the drug. As for sulfaethylthiadiazole, the continued presence of the drug in the blood results from delayed absorption accomplished by coating various-sized granules of the drug with certain waxes, thereby permitting absorption over a larger area of the

intestinal tract. All the drugs in this group are eventually excreted chiefly by the kidney, with lesser amounts excreted into other secretions as mentioned above.

The so-called nonabsorbed sulfonamide drugs have relatively little usefulness in pediatric therapeutics and will, therefore, be considered briefly and in rather general terms. These drugs are not bacteriostatic in the form in which they are administered. They are converted to the active compound, usually sulfathiazole, sulfacetamide or sulfapyridine, by the action of bacteria in the large bowel. Since relatively little absorption of sulfonamide drugs occurs from the large bowel, high concentration of the agents acts locally on the bacterial flora. It should be noted, however, that some systemic absorption can occur, and the administration of such preparations is accompanied by the possible development of the toxic reactions subsequently described in more detail.

After absorption from the gastrointestinal tract the sulfonamide drugs are rapidly distributed to all tissues of the body. For practical considerations, equilibrium between the serum and the body tissues is reached in approximately two to four hours. The concentration of sulfonamide in the cerebrospinal fluid deserves special mention. In the absence of meningeal inflammation, the concentration of sulfonamides in cerebrospinal fluid, with the exception of sulfadiazine, is low. In the presence of meningeal inflammation, however, the agents described here can reach bacteriostatic levels for sensitive bacterial species. Generally only the parenteral use of sulfadiazine or sulfisoxazole is recommended for the treatment of meningitis.

The antibacterial activity of sulfonamide drugs depends solely upon the amount of free sulfonamide available. There are wide variations between different agents in the free sulfonamide concentration which can be measured in blood, body fluids or tissues. The concentration of free sulfonamide varies with each compound, being dependent upon the amount bound to serum proteins, chiefly albumin, and also to the rate of acetylation, oxidation and other metabolic processes which convert the free drug into inert compounds. These latter changes occur chiefly in the liver.

The mechanism by which the sulfonamide drugs inhibit bacterial growth is not completely known. The widely accepted theory proposed by Woods[7] and Fildes[3] is that the sulfonamide drug prevents bacteria from utilizing para-aminobenzoic acid (PABA), or substances derived from it, in essential metabolic processes. A state of bacteriostasis is then reached, and the bacteria are subsequently destroyed by phagocytosis as well as by other tissue and humoral defense mechanisms. Under normal circumstances sulfonamide drugs are not bactericidal.

Bacteria not inhibited by sulfonamides are usually not dependent

upon exogenous sources of PABA for their normal growth. This observation seems to hold for most species of sulfonamide-resistant bacteria, although there are other proposed explanations for innate or acquired resistance. In general, bacterial species or strains which are not inhibited by one sulfonamide agent are not inhibited by an equally potent concentration of other sulfonamide drugs which have a para-amino group in the compound and are antagonized by PABA. Thus, in instances in which no favorable clinical response has occurred after the administration of one sulfonamide drug, there is no reason to expect that the substitution of another sulfonamide agent will cause improvement.

There is a large mass of data obtained chiefly from animal experiments, but also from human patients after infections, which indicate that the administration of sulfonamide drugs does not reduce the production of antibodies in the host. Further, the administration of sulfonamides does not alter the normal bactericidal activity of serum. An excellent general review of sulfonamide drugs is presented in the text by Goodman and Gilman.[4]

TOXICITY

Because sulfonamide drugs can cause a variety of toxic reactions, ranging from those of no practical consequence to those with fatal outcome, it is extremely important that these reactions be well known to all. Some of these reactions can be prevented or detected while reversible so that serious reactions are infrequent. A review by Lehr[6] summarizes the clinical toxicity of sulfonamides. The toxic reactions following the administration of sulfonamide drugs vary with each compound. None of the drugs listed in Table 15 causes an undue number of toxic reactions, but each of these agents can produce the reactions to be described below. In addition to variation in frequency of toxic reactions according to the individual compound, the amount and duration of administration of each compound are significant, since more reactions are likely to be noted with the use of large amounts of these drugs or with their prolonged administration. Of significance in the frequency of reactions is the solubility of the free and conjugated sulfonamide in the normal pH range of human urine.

Factors related to the patient also influence the frequency of toxic reactions. Age is an important factor. Newborn infants are particularly sensitive to the parenteral administration of sulfisoxazole (Gantrisin) and perhaps sodium sulfadiazine. An increased frequency of kernicterus has been observed when these drugs are given. Further, the newborn infant is more likely to show other reactions because of immature hepatic and renal function. In older patients reduced renal function,

from earlier or present disease, also increases the likelihood of toxic reactions. Other significant patient factors influencing the occurrence of reactions include the state of hydration and nutrition, previous administration of sulfonamides and the presence of an allergic diathesis.

One of the principal toxic reactions is the precipitation of sulfonamide crystals in the kidney, ureters and lower urinary tract. Although crystalluria may not produce any symptoms, it can result in mechanical obstruction in the kidney or lower urinary tract. On occasion, anuria with severe renal damage or even renal failure has been noted. Such serious reactions are fortunately infrequent, and their occurrence can be reduced if an adequate urinary output is maintained. Certain sulfonamides, such as sulfisoxazole, sulfadimetine or mixtures of several sulfonamides, are less likely to cause such reactions. Other serious and even fatal renal reactions have been noted, presumably the result of a hypersensitivity state.

A large variety of hypersensitivity reactions has been noted following the administration of sulfonamides. Drug fever may be noted especially between the seventh and tenth days of therapy, but is occasionally noted after the drug has been discontinued. The fever may be accompanied by rashes, malaise and chills. These symptoms usually subside when the drug is withdrawn. Drug rashes may follow the administration of these agents. Most of these eruptions subside promptly after cessation of therapy, although, occasionally, serious lesions such as pemphigus have been reported. Contact reactions following the application of sulfonamides to the skin and mucous membranes are frequent and may be serious. The author has observed three nearly fatal instances of exfoliative dermatitis following the application of small amounts of sulfathiazole to the skin. There are no good reasons why topical applications should be recommended except perhaps to the conjunctiva, which seems to be singularly tolerant of these drugs.

Other sensitization reactions, such as vascular lesions, parenchymal damage to the liver or kidneys, and so on, may occur, but fortunately these serious reactions are infrequent.

Toxic reactions involving the blood-forming organs are fortunately uncommon after the administration of the presently used agents, but these reactions may occasionally be fatal. Neutropenia and agranulocytosis can be detected early if frequent white blood cell counts are performed. Cessation of therapy is usually followed by prompt recovery. Aplastic anemia and thrombocytopenic purpura are less common than the previously mentioned reactions, but are less likely to improve spontaneously. Acute hemolytic anemia may develop after the administration of sulfonamides. This is one of the few reactions observed more frequently in children than in adults.[6] Further, it occurs more frequently in Negro than in white children. Most, if not

all, instances of acute hemolytic anemia occur in patients having a congenital deficiency in the enzyme glucose-6-phosphate dehydrogenase. Persons who have shown this reaction should not subsequently receive sulfonamides or compounds such as primaquine, nitrofurazone, naphthalene, and the like.

Many other toxic reactions can occur, although they are not as common as those described above. These reactions include hepatitis, cyanosis, disturbances in the sensorium, peripheral neuritis and others.

Note that certain toxic reactions commonly following the administration of antibiotic drugs rarely, if ever, follow the use of sulfonamides. These reactions include immediate anaphylactic reactions, as with penicillin; eighth nerve damage, as with streptomycin, neomycin and kanamycin; alteration of bacterial flora and development of extensive moniliasis, as with the broad-spectrum antibiotic agents.

The over-all frequency of toxic reactions with the various agents is difficult to evaluate. Many of the extensive reviews have dealt chiefly with reactions in adults.[5, 6] The frequency of reactions in children is definitely less with the exceptions of kernicterus and acute hemolytic anemia. No single sulfonamide agent is so devoid of toxic reactions that it can be recommended over the other drugs. Sulfadiazine, sulfisoxazole (Gantrisin), sulfadimetine (Elkosin) and mixtures ("Triple Sulfonamides") have approximately the same low frequency of toxic reactions, probably less than 5 per cent for all reactions and probably well under 0.1 per cent for serious reactions. The relatively limited experience with the "long-acting" sulfonamides makes the evaluation of their toxicity potentials difficult. Concern over the consequences of the accidental ingestion of a large dose by the patient or a sibling has led to the limitation of their use in our institution.

In the past it was important to find ways to counteract the toxicity reactions following the administration of the sulfonamide drugs if treatment was to continue. At present only the severe reactions such as hemolytic anemia or aplastic anemia demand special treatment. The milder reactions such as skin eruptions and drug fever can be circumvented by stopping the administration of the sulfonamide drug and, if further treatment is still necessary, administering an appropriate antibiotic drug.

If a suspected or definite toxic reaction follows the administration of a sulfonamide drug, the use of that drug should immediately be suspended and another antimicrobial drug, *but not another sulfonamide*, should be given if further treatment is required.

INDICATIONS

As new agents have become available for therapeutic use, the importance of the sulfonamide drugs in the management of human in-

fections has decreased. Although human infections with many bacterial species are favorably influenced by sulfonamide therapy, there are only two serious infections, meningococcal and perhaps nocardial,[1] for which the sulfonamide drugs are regarded as the most effective therapeutic agents. Sulfadiazine may be considered the drug of choice in the prevention of recurrences of rheumatic fever in persons who are sensitive to penicillin.

Sulfonamide drugs may be useful in combination with other agents in the treatment of certain diseases such as actinomycosis, blastomycosis, brucellosis, influenzal meningitis, pneumococcal meningitis, tularemia, and others, although the infrequency with which such infections occur makes precise evaluation of therapy difficult. Many strains of shigella species are as sensitive to sulfonamides as they are to antibiotic agents, but some sulfonamide-resistant strains have been isolated in epidemics of shigella dysentery.

Although there is no doubt that many infections, e.g. pneumococcal or group A beta hemolytic streptococcal infections, are successfully controlled by the administration of sulfonamide drugs, another agent, penicillin, is definitely superior to the former drugs. Many other illustrations can be cited; e.g. infections caused by *Escherichia coli* or staphylococci are more likely to respond to the administration of the tetracycline drugs or erythromycin, respectively, than to sulfonamide compounds. It is unnecessary to list other examples. As the critical appraisal of the therapy of bacterial infections has improved, it has become increasingly apparent that the sulfonamide drugs, although useful therapeutic agents, are no longer the best agents for the treatment of most bacterial infections. The continued widespread use of these drugs persists chiefly because they are less expensive than other, more effective antimicrobial agents.

CONTRAINDICATIONS

Sulfonamide drugs should not be used in the treatment of viral infections or in bacterial infections in which other, more effective drugs are available. The sulfonamide drugs are not effective in the treatment of salmonella, tuberculous, spirochetal, rickettsial and many other infections.

Extreme caution should be used if these agents must be administered to premature or full-term newborn infants because of the potential hazard of the development of kernicterus.

Sulfonamide agents will not be effective in the treatment of infections which produce purulent collections.

Sulfonamide drugs are contraindicated in patients who have previously had a toxic reaction to the same or another sulfonamide com-

pound. Further, their use is contraindicated in patients who have a deficiency in glucose-6-phosphate dehydrogenase.

SUMMARY

An attempt has been made to review the present status of sulfonamide therapy for the treatment of infections in infants and children. Other, more effective agents are available for most of these diseases.

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AMPHOTERICIN B

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Increasing awareness of systemic disease caused by fungus infections has led to the development of effective antifungal agents. One of the most promising undergoing clinical trials in various diseases is amphotericin B. The use of this drug for treatment of deep mycotic infections has been fairly extensive. It is worth while to review the indications for the use of the drug from extensive clinical reports and personally treated cases.

Amphotericin B is one of two antibiotic fractions isolated and reported by Gold et al.[2] from an unidentified species of streptomyces obtained from soil near the Orinoco River in Venezuela. The early experience with this new drug soon established the lack of effectiveness of oral administration of the drug, since it is poorly absorbed from the gastrointestinal tract. Studies in vitro, however, have shown that as little as 0.5 mg. per milliliter of medium is sufficient to inhibit growth of *Blastomyces dermatitidis*. Numerous clinical trials with small intravenous dose schedules have proved the effectiveness of the drug.[7] Bioassay methods developed by McNall et al.[6] were used in initial clinical trials. It became apparent, however, that the usual concentration, by this method, was approximately 48 to 68 micrograms per milliliter 24 to 36 hours after the administration of 50 mg. of amphotericin B intravenously over a 6-hour period. The routine use of the bioassay method has not been essential in clinical use.

The mode of action of amphotericin B centers about the over-all oxidative metabolic processes of the yeast phase in which higher concentration exerts an inhibitory effect.[1]

DOSAGE

Tolerance to amphotericin B varies with the individual patient and should be adjusted to the specific response of the patient. The initial

daily dose of 0.25 mg. per kilogram of body weight is gradually increased until the maximum dose which is successfully tolerated is attained.[3] The dose should be the highest level not accompanied by toxic manifestations. Accordingly, a simplified daily schedule for an adult patient is as follows:

1st day—20 mg. in 200 ml. of 5% g/w
2nd day—30 mg. in 300 ml. of 5% g/w
3rd day—40 mg. in 400 ml. of 5% g/w
4th day—50 mg. in 500 ml. of 5% g/w

Should systemic reactions occur, the previously tolerated dose is given intravenously every other day until a total of 1 gm. has been administered. A period of two weeks has been utilized to afford a rest between planned courses of therapy. It has been found practical to give the intravenous amphotericin B every other day over a four- to six-hour period. By this method, nutrition is maintained, nitrogen retention is less, and the effectiveness of the drug is not altered. In the acutely ill patient, however, it is preferable to administer the drug in lesser amounts on a daily schedule. A daily dosage of 100 mg. has been given for several days on occasion, but it has been associated with more severe systemic toxicity, mild secondary anemia, and nitrogen retention.

TOXICITY

Systemic manifestations, consisting of anorexia, headache, chills and fever, are frequently encountered during the intravenous administration of amphotericin B. These reactions subside with the concomitant use of antipyretics and antihistamines given on a three- or four-hour schedule. When severe reaction occurs, the intravenous infusion is interrupted and then resumed at a lower dosage the following day. A solution of 5 per cent dextrose in water is attached to a Y tube, and the infusion needle is flushed at intervals to minimize the hazard of thrombophlebitis. The powdered drug is prepared by dilution in 5 per cent glucose in water so that the final concentration of 0.1 mg. per milliliter should not vary, since buffer also will be altered by dilution. Adherence to proper concentration and dilution of the buffer has minimized the severity of thrombophlebitis.

The evaluation of this antifungal agent has shown that rising blood urea nitrogen nearly always occurs during therapy with higher concentrations. Routine urinalysis will reveal occasional granular casts and traces of albumin. Therapy should be interrupted when the blood urea nitrogen reaches 30 mg. per milliliter. Renal function regularly returns to normal after discontinuance of amphotericin B therapy. Liver function studies have shown only minor alterations and can be followed by thymol turbidity tests and serum transaminase levels.

Among the miscellaneous side effects of the drug are occasional instances of anemia during prolonged therapy and gastrointestinal cramping and diarrhea. A few patients have had a maculopapular rash. Since amphotericin B has appreciable toxicity, the drug should be given only to patients in whom a diagnosis of susceptible mycotic infection is proved by smear or culture. There is no adequate justification for use of the drug in vague undiagnosed conditions merely because the skin test for one of the fungi may be positive. Therapy with this drug should proceed uninterrupted for several weeks, since early remission cannot be expected. It is preferable to attain a dose of drug which can be tolerated by the patient with minimal gastrointestinal symptoms, systemic symptoms, and blood urea nitrogen retention.

INDICATIONS IN SPECIFIC MYCOTIC DISEASES

Histoplasmosis

The clinician is confronted with these forms of disease: the acutely ill, toxic patient with acute pulmonary histoplasmosis, chronic pulmonary histoplasmosis, or an undiagnosed "coin" lesion of the lung. The acute pulmonary infection is usually a benign infection, only rarely going on to a more progressive disease. Evidence of dissemination of histoplasmosis, as proved by culture of a mucous membrane lesion or the clinical course, is an indication for treatment with amphotericin B. Chronic pulmonary histoplasmosis is characterized by cavities of the upper lobes. This form progresses gradually over several years with remissions and exacerbations and progressive loss of pulmonary tissue.[9] If the disease is untreated, the prognosis is poor; in the treated cases sputum conversion occurs in two to three weeks. The optimum total dose of 1.5 to 2 gm. of amphotericin B has produced favorable therapeutic effect, although cure with eradication of lesions has not been obtained. Residual bullae are the usually late sequelae. The excised coin lesion from the parenchyma of the lung with concentric rings and necrotic center containing *H. capsulatum* does not require treatment with amphotericin B.

Blastomycosis

This fungus disease occurs as primary inoculation blastomycosis and systemic disease. It seems probable that the disseminated form of the disease begins as a primary pulmonary infection by inhalation of the causative agent. Commonly, the pulmonary process is a non-specific pneumonitis, and the histologic study of autopsy material and the resected surgical specimens reveals small microabscesses surrounding clusters of organisms. Residual cavities with positive sputum have responded well with clearing of the pulmonary lesions and sputum

conversion with a total dose of 1.5 to 2 gm. of amphotericin B.[7] Planned excisional surgery of residual cavitary lesions should follow the first 1-gm. course of therapy with amphotericin B. Thereafter an additional gram should be given. Not enough attention has been directed to blastomycosis of the genitourinary tract with a focus of infection in the prostate. Since the patient with urine cultures of prostatic secretions positive for *Blastomyces dermatitidis* has an unusually resistant infection, the total dose of amphotericin B should approach 3 gm.

Coccidioidomycosis

Favorable response to amphotericin B has been well documented in chronic pulmonary coccidioidomycosis.[11] Planned excisional surgery of residual cavitary lesions should follow the first 1-gm. course of therapy with amphotericin B. Thereafter an additional gram should be given. Particularly significant is the closure of cavities which occur as complications following pulmonary resection. The total dose is approximately 2 gm. over 6 to 8 weeks. For the disseminated form of coccidioidomycosis, intravenous amphotericin should continue until clinical response is attained, or the total administered dose is 2.5 to 3 gm.

Cryptococcosis

Increasing reports[8] verify the effective therapy with amphotericin B in the treatment of meningitis and meningoencephalitis due to *Cryptococcus neoformans*. Littman[4] has reported the use of concomitant intrathecal amphotericin B every other day with intravenous administration of the drug. Experience with this mode of administration is limited.

Moniliasis

Similar schedules of administration of amphotericin B in total dose approaching 3 gm. have been given patients with disseminated moniliasis.[5] Apparent reversal of blood stream infection has occurred in approximately half of the cases treated. Failure has occurred in the remaining cases.[10] The effective action of the drug for this mycotic infection has not been well substantiated.

SUMMARY

Amphotericin B is a broad-spectrum antifungal drug for use in the treatment of pathogenic mycotic fungi in man. The method of ad-

ministration and the approximate total dose for the common mycotic infections have been outlined. Toxic manifestations occur in most instances, but the severity of the reactions does not prevent the effective use of the drug.

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GAMMA GLOBULIN

Studies on the Antibacterial Properties of Pooled Human Gamma Globulin

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Whereas passive immunization was once the only means for specifically controlling deep bacterial infections,[11] it has justifiably been replaced almost completely by the arts of chemotherapy. In recent years, however, the concept of the immunotherapy of bacterioses has been revived through various and new applications of pooled normal human gamma globulin (GG). That such immune therapy has respectable merit, when used alone or in conjunction with antibiotics, can be adduced from a number of laboratory and clinical reports.[2, 4, 5, 9, 10, 12, 14-19]

Nevertheless, unlike the rationales for usage which have been established for antibiotics, only limited or empiric knowledge is available to the clinician who may desire to use GG against a bacterial infection. It is known, for example, that the administration of GG as an antibacterial is particularly indicated for diagnosed GG deficiency states[8] and an immunologically similar condition recently designated as the "antibody deficiency syndrome."[1] The latter disease, parenthetically, teaches that a "normal" blood level of gamma globulin is by no means proof of a "normal" antibody capacity.

It is suggested, moreover, that GG administration—often as an adjunct to other measures—can be of distinct benefit in conditions in which immunologic incompetence or inadequacy is suspected. This circumstance might pertain to the newborn, on the one hand, and to the very elderly on the other. It might also apply to those who are debilitated, who are suffering from especially severe, acute disease, or who are the victims of refractory infections, particularly those caused by certain antibiotic-resistant bacteria.

Beyond these aforementioned generalities, a regrettable paucity of signposts exists to guide GG usage as an antibacterial agent. Only limited

data are available, for example, on dose regimens. Fisher, in another publication,[7] has attempted to formulate some principles of GG administration based upon experiments in mice. The essential observations and interpretations of these studies on GG "pharmacology" will be described later as part of this report.

Another aspect of practical importance which has not yet been fully elucidated pertains to the antibacterial spectrum of GG. More specifically, the question has not been answered adequately as to which species and types of bacteria are likely to be susceptible to available sources of pooled normal human gamma globulin derived from donors in the continental United States. Although a modest amount of such data has been published,[6] the presentation of an expanded spectrum is another purpose of this communication.

EXPERIMENTAL OBSERVATIONS

The experiments in question depend upon the demonstration of *anti-infection antibodies* in gamma globulin, as distinguished from other manifestations of bacterial antibodies: agglutinins, precipitins, antitoxins, and the like. This aspect has particular relevance to the validity of the antibacterial spectrum of GG to be described.

Since the detailed methodology of these studies has been described elsewhere,[6, 7] it will not be repeated here. Where indicated, pertinent information on technique will be given in the discussion of certain experiments.

Tests related to the antibacterial spectrum of GG involve the intraperitoneal injection of a single dose of GG, given at the time of intraperitoneal challenge with 100 LD_{50} of the test organism. All experiments were performed in 6- to 8-week-old Carworth Farms CF-W or CF-1 mice. The GG used throughout consisted of samples of different production lots of pooled normal human gamma globulin ("Immu-G," Parke-Davis).

Experiments on Dose Regimens

Severity of Infection. The data in Table 16 serve to emphasize the well known fact in therapeutics that proportionally more intensive treatment is required for increasingly severe infections. In the case of GG dosages, the data reveal a straight-line relation between the 50 per cent protective dose and the logarithm of the number of challenge staphylococci. Similar results have been obtained in experiments with other pathogens.

Route of Administration. The experiment summarized in Table 17 pertains to a highly acute staphylococcal infection, wherein death occurred among untreated controls within 18 hours after challenge intra-

TABLE 16. *Influence of Size of Challenge on Gamma Globulin Activity against an Acute Staphylococcal Challenge*

LD_{50} IN CHALLENGE	APPROXIMATE 50% PROTECTIVE DOSE GAMMA GLOBULIN, MG./KG.*
10^2	4
10^3	33
10^4	250
10^5	2000

* Single intraperitoneal dose at time of intraperitoneal challenge with *S. aureus* (Smith).

peritoneally. That GG treatment was most effective when given directly into the peritoneal cavity was a strong indication of its relatively slower systemic distribution from subcutaneous and intramuscular injections. It also indicated, for acute disease, the need for achieving the maximum concentration of GG in the shortest time at the site of infection. This result may explain why intraperitoneally injected GG was even more effective than that given intravenously, when the disease originated as a peritonitis.

No such dissimilarity of results occurred in a systemic subacute streptococcal infection, wherein the median death time in untreated mice was five to seven days. Under such conditions, as shown by the results given in Table 18, practically equal therapeutic effects were obtained whether GG was administered intraperitoneally, intravenously, subcutaneously or intramuscularly. It can be assumed that an equilibrium of GG in the mouse was attained from all four routes well before the infection became lethal.

The importance of delivering GG directly to the site of infection is illustrated by the data given in Table 19. In this experiment, particularly with respect to the subcutaneously induced infection, GG injected subcutaneously into the focus of infection was nearly 10 times more effective than GG given subcutaneously elsewhere. This phenomenon suggests a "local" activity of GG.

FREQUENCY OF DOSAGE. With a slowly progressing streptococcal infection as an experimental model, it was found that a given dose of GG as a single injection was ultimately as beneficial as divided doses. The

TABLE 17. *Influence of Route of Administration of Gamma Globulin on Activity against an Acute Staphylococcal Challenge*

ROUTE OF GAMMA GLOBULIN ADMINISTRATION	APPROXIMATE 50% PROTECTIVE DOSE GAMMA GLOBULIN, MG./KG.*
Intraperitoneal	4
Intravenous	80
Subcutaneous	200
Intramuscular	>1000

* Single dose at time of intraperitoneal challenge with 100 LD_{50} *S. aureus* (Smith).

TABLE 18. *Influence of Route of Gamma Globulin Administration on Activity against an Established Subacute Streptococcal Infection**

ROUTE OF GAMMA GLOBULIN ADMINISTRATION†	SURVIVORS/TOTAL	PER CENT SURVIVORS
Untreated controls	4/40	10.0
Intraperitoneal	25/40	62.5
Intravenous	23/40	57.5
Subcutaneous	24/40	60.0
Intramuscular	25/40	62.5

* Induced subcutaneously with 100 LD_{50} *Strep. pyogenes* (C-203).
† Single dose of 1000 mg./kg. 2 days after challenge.

TABLE 19. *Influence of Route of Administration of Gamma Globulin on Activity with Respect to Site of Infection Induced with 100 LD_{50} Streptococcus Pyogenes (C-203)*

SITE INFECTION INITIATED	SITE OF GAMMA GLOBULIN ADMINISTRATION	APPROXIMATE 50% PROTECTIVE DOSE GAMMA GLOBULIN, MG./KG.*
Intraperitoneal	Intraperitoneal	180
Intraperitoneal	Subcutaneous	2000
Subcutaneous	Intraperitoneal	200
Subcutaneous	Subcutaneous, same locus as infection	35
Subcutaneous	Subcutaneous, opposite to locus of infection	260

* Single dose at time of challenge.

TABLE 20. *Influence of Single and Divided Doses of Gamma Globulin on Activity against a Subacute Streptococcal Infection**

TOTAL DOSE OF GAMMA GLOBULIN, MG./KG.	DAILY DOSE OF GAMMA GLOBULIN, MG./KG.†	NUMBER OF DOSES	PER CENT SURVIVORS‡
2000	2000	1	91
2000	1000	2	92
2000	667	3	86
2000	500	4	80

* Induced subcutaneously with 100 LD_{50} *Strep. pyogenes* (C-203).
† Intraperitoneal.
‡ Based on groups of 80 mice per regimen; 4% survivors among untreated controls.

results presented in Table 20 indicate that the principal determinant of therapeutic efficacy was the total GG dose rather than the number of divided doses.

DURATION OF ACTIVITY. The experimental results depicted in Figure 12 indirectly reveal the relative persistence of GG in the mouse after different routes of administration. The basic design of these tests consisted in the use of a single dose of GG, which, from previous experience, would provide between 50 and 80 per cent protection for a given route of administration. In those experiments in which GG was injected intramuscularly, for example, a large number of mice of similar age, sex

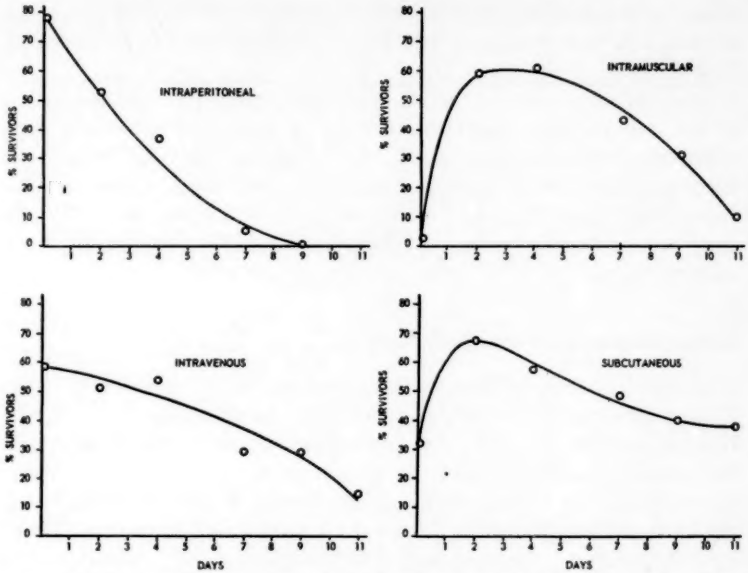

Fig. 12. Duration of protective activity of gamma globulin given by various routes against an acute staphylococcal infection. The abscissa for each graph represents the number of days between the injection of a single dose of gamma globulin and subsequent challenge. Each point on each curve was derived from a group of 60 to 80 mice, and the survival percentages were pooled from 3 to 4 replicate experiments. There were 2 per cent survivors among untreated control mice.

and weight was subdivided into six groups. Group 1 was given a single dose of GG 11 days before challenge; group 2 was given the same dose 9 days before challenge; group 3 was treated 7 days before challenge; and so forth through group 6, which was dosed simultaneously with the challenge. By this procedure all the mice were challenged on the same day.

Similar procedures were followed for the three other routes of GG administration. An acute staphylococcal challenge, intraperitoneally injected, was utilized throughout. It should be noted that this infection developed rapidly (within 6 hours) to an overwhelming systemic disease having a fatal outcome in untreated mice within 18 hours. Thus a fairly sharp cut-off point was provided to measure the residual protective activity of GG within a narrow period.

The curves drawn in Figure 12, based on the foregoing method, show firstly that the most sustained action of GG occurred after a single subcutaneous dose. As a rough estimate, it would appear that GG had a half-life of about 10 days when given subcutaneously. The same measure for intramuscular GG was about nine days; for intravenous GG about 8½ days; and about 3 days for intraperitoneal GG. Since similar

values were noted in replicate tests using other bacteria, these half-life estimates do not pertain strictly to the staphylococcus-protective antibody in GG.

A second phenomenon, which was qualitatively predictable, related to the time to reach maximum activity. As expected, immediate peak effectiveness followed intravenous and intraperitoneal GG dosing, the latter doubtless due to the previously described "local" action of GG. In contrast, about 1½ days were needed to reach maximum activity after a subcutaneous dose, and between 2 and 4 days for an intramuscular dose.

Antibacterial Spectrum of Gamma Globulin

A qualitative rating of bacterial susceptibility to GG is shown in Table 21, derived in part from previously published data.[6] As mentioned earlier, this information is based solely upon the protective activity of GG in experimentally infected mice. In this table the symbol "O" indicates no measurable protection from GG up through total doses of 4000 mg. per kilogram (equivalent to 25 ml. per kilogram of 16 per cent gamma globulin solution). In like manner, the designation "±" connotes weak but reproducible activity at high doses, and so forth through "++++," which indicates definite protective activity at dosages as low as 3 mg. per kilogram (approximately 0.004 ml. of 16 per cent gamma globulin per kilogram).

DISCUSSION

The question of the degree of relevance of these experiments to human therapy cannot be answered at this time. Although there are many obvious dissimilarities between mice and human beings, the particular value of the laboratory mouse is well established for providing useful knowledge for the understanding and control of bacterial infections in man. Indeed, nearly all the principal antibacterial agents used today in human medicine were developed to a considerable extent from experiments in mice. A similar situation pertained earlier in this century on the use of various antibacterial serums derived from hyperimmunized animals.

With these points in mind, one may proceed toward a conservative synthesis from these studies of some principles for GG usage.

1. *Larger doses of gamma globulin are needed to control larger numbers of bacteria.*

This observation is also known as the "inoculum size" effect, often seen in tests in vitro of synthetic and antibiotic antibacterials. In the case of GG, this phenomenon may be due to the affinity of a certain number of antibody molecules per bacterial cell, coupled with the

TABLE 21. *Antibacterial Spectrum of Human Gamma Globulin in vivo*

SPECIES	TYPE	RELATIVE GG SUSCEPTIBILITY
Gram-negative:		
Aerobacter aerogenes	1 strain	+
Escherichia coli	MGN-1[a]	++++
	MGH-2[a]	0
	MGH-3[a]	++++
	MGH-4[a]	0
	MGH-5[a]	0
	055:B5[b]	±
	086:B7[b]	++++
	0111:B4[b]	±
	0119:B14[b]	++++
	0127:B8[b]	+++
Klebsiella pneumoniae	2 strains	0
Pasteurella multocida	1 strain	0
Proteus mirabilis	1 strain	+
Proteus vulgaris	2 strains	+ to +++
Pseudomonas aeruginosa	1–19–1	++++
	10–14–1	++
	8–15–2	++
	8–15–5	0
	9620	+++
	6–28–17	0
	6–17–1	+++
	10–3–20	±
	12–11–11	0
	9–20–8	0
Salmonella typhimurium	2 strains	+
Shigella flexneri	1 strain	0
Acid-fast:		
Mycobacterium tuberculosis	H37Rv	0
Gram-positive:		
Diplococcus pneumoniae	Type I	+
Staphylococcus aureus	Phage 80/81 (2 strains)	0
	Phage 44A (2 strains)	++++
	Phage 71/42D	++++
	Phage 3B/71	++++
	N.T. (5 strains)[c]	++++
Streptococcus faecalis	1 strain	0
Streptococcus pyogenes	Group A, type 14	++
Streptococcus salivarius	1 strain	+++
Streptococcus species	Group B	0
	Group C	0

[a] Human adult virulent strains; not of a special serotype.
[b] Infantile diarrhea strains; enteropathogenic serotypes.
[c] "N.T.": not phage typable.

knowledge that a limited amount of such antibody is present in a given volume of normal GG.

2. *Fulminating systemic infections may require a subcutaneous or intravenous dose of gamma globulin.*

Mainly because of their high molecular weight, the antibodies in GG do not attain their maximum systemic distribution in man until two days after an intramuscular injection.[8] If GG, on the one hand, is to be used prophylactically or for the treatment of mild, subacute disease, this two-day period may be acceptable. If, on the other hand, the circumstances of fulminating disease demand the prompt adjuvant benefits of passive immunity, then consideration might be given to an intravenous injection of GG. Although warnings have been stated against the intravenous administration of GG because of side reactions,[8] it has been shown that under certain conditions this route can be used cautiously without serious consequences.[13]

A more acceptable alternative to an intramuscular injection, when time is important, is the subcutaneous route. As suggested by the graph in Figure 12, an immediate and respectably high level of GG activity was noted from subcutaneously injected GG. According to Gross, Gitlin and Janeway,[8] GG may be given by this route with the same relative impunity as an intramuscular dose.

3. *Against localized disease gamma globulin may be most effective on direct instillation.*

The experiments on this aspect, summarized in Table 19, suggest the local instillation of GG where practicable. When the site of disease is confined to an accessible body cavity—either of natural or of pathologic origin—the direct application of GG to that area may provide a better therapeutic result than a "remote" parenteral injection.

4. *Gamma globulin activity may be more prolonged from a subcutaneous than from an intramuscular injection.*

Although this supposition has been established for mice in many experiments, no such evidence is available from data on human treatment. Until such data have been acquired, the relative merits of the two aforementioned routes of injection in human beings are largely conjectural. This limitation would apply both to persistence and to rates of systemic distribution in man of a subcutaneous dose vis-à-vis that given intramuscularly.

5. *Gamma globulin is in general most active against those bacteria which are normal inhabitants of man.*

It was previously stated[6] that the presence of these specific antibodies in GG is largely the result of a lifetime of intimate contact with commonly occurring bacteria. The antibodies in question probably arise mainly from the antigens present in the normal flora of the skin, upper respiratory tract, and the intestinal tract. A lesser source might be the occurrence of overt or occult infections.

It should be mentioned parenthetically that individual serums from normal adults exhibit the same antibacterial spectrum as that given in Table 21 for pooled GG. This observation, accrued from experiments

performed here and published in part,[3] tends to substantiate further the concept of "normal" specific antibodies in GG. That is, it is unlikely that a significant amount of a given antibody in a production lot of GG (pooled from over 10,000 donors) comes from a few hyperimmune persons.

Of special interest and potential value is the evidence that GG is—with few exceptions—rich in antibodies against some "problem pathogens," notably *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The frequency and seriousness of infections caused by these species would recommend the adjunctive application of GG for their treatment. As stated earlier, such a measure deserves consideration when immunologic deficiencies are known or suspected.

A provocative observation was the fact that GG exhibited variable activity among different types of the same species. Because of the limited availability of suitable mouse-virulent strains, intraspecies analyses were run only for *Escherichia coli*, *Ps. aeruginosa* and *Staph. aureus*. The ratings in Table 21 indicate differences in GG susceptibility between different types within each of these 3 species. Speculations on the basis of this phenomenon will be reserved for another occasion. It is evident, however, that an element of uncertainty on GG usage has been introduced. Therefore, until suitable clinical data can be obtained for correlation with mouse test results, it can only be proposed that GG may be effective against a respectable number of types of *E. coli*, *Ps. aeruginosa* and *Staph. aureus*. Although this kind of variability may be the basis for the opinion that GG is no "cure-all,"[18] it is not sufficient to obviate the administration of GG when indicated clinically for bacterial disease.

In conclusion, it may be an overlooked fact that the very existence of most infections is, by definition, a sign of some host defense insufficiency. Any steps taken toward the correction of this state should logically enhance the conventional therapeutic effort and increase the probability and rate of recovery. At present, perhaps the most practicable means available for an immediate immunologic augmentation lies in the administration of pooled human gamma globulin.

SUMMARY

Experimental data from tests in mice are presented to help define the antibacterial behavior of pooled human gamma globulin. The salient observations were that a subcutaneous injection may provide a more rapid and a more sustained activity than an intramuscular dose; that intravenous treatment may be considered in urgent situations; and that gamma globulin has outstanding but variable activity against common bacterial pathogens.

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ERYTHROMYCIN

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Erythromycin is one of a group of antibiotics called macrolides which are related by their common nucleus, a macrocyclic lactone. These antibiotics are shown in Table 22.

TABLE 22. *Macrolides Group of Antibiotics*

Erythromycin	Streptomyces erythreus
Carbomycin	Streptomyces halstedii
Spiramycin	Streptomyces ambofaciens
Oleandomycin	Streptomyces antibioticus

Though isolated from strains of streptomyces and having a similar nucleus, they differ because of the "sugars" in their side chains (Table 23).

TABLE 23. *Erythromycin-Oleandomycin Moieties*

	PART III SUGAR	PART I NUCLEUS	PART II SUGAR
Erythromycin	Cladinose	Erythronolide	Desosamine
Oleandomycin	Oleandrose	Oleandolide	Desosamine

Two of the macrolides are available commercially in the United States. Carbomycin has been shown to be relatively ineffective clinically. Spiramycin is available at present only in Europe. Only erythromycin will be considered in this discussion.

CHEMISTRY

Erythromycin was first produced, purified, and used clinically in 1952 by McGuire and his associates. Three detailed reviews are avail-

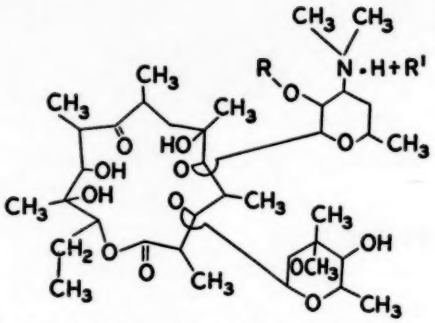

Fig. 13. Structural formula of erythromycin.

	R	R^1
Erythromycin	H	
Propionyl erythromycin	CH_3CH_2CO	
Erythromycin estolate	CH_3CH_2CO	$C_{12}H_{25}OSO_3$
Erythromycin stearate	H	$C_{17}H_{35}COO$
Erythromycin ethyl succinate	$CH_3CH_2OOCCH_2CH_2COO$	

able.[18, 22, 39] Wiley et al.[101] have reported the structural formula of erythromycin. The propionyl ester of erythromycin, developed by Stephens and others,[87, 88] was further modified by preparation of its lauryl sulfate salt. The complete formula for erythromycin and its derivatives is shown in Figure 13.

Erythromycin estolate is the generic name given to designate the lauryl sulfate salt of propionyl erythromycin.

Erythromycin estolate is practically tasteless and retains its potency at the pH of gastric acid for prolonged periods. Studies on the mechanism of drug absorption by Schanker et al.[44, 78] have shown that organic compounds are probably absorbed in the un-ionized form; therefore the pK_a of a substance has a bearing on its ionization and absorption in the intestinal tract. The pK_a of erythromycin estolate (6.9), as compared with that of erythromycin (8.6), may have an influence on the improved absorption of this new derivative when administered orally.

BACTERIOLOGY

The antibacterial spectrum of erythromycin is more extensive than that of penicillin, since it includes the clostridia and diphtheria bacilli, hemophilus, rickettsia and brucella. Gram-negative bacteria of the intestinal tract are not usually considered susceptible. Nevertheless concentrations may be achieved in the urine that will be effective against many of the urinary tract pathogens. The spectrum in vitro of erythromycin is shown in Table 24.

TABLE 24. *In Vitro Spectrum of Erythromycin*

ORGANISM	RANGE	MOST STRAINS
Streptococcus (pyogenic group)	0.007– 0.62	0.04
Diplococcus pneumoniae	0.003– 0.4	0.03
Staphylococcus aureus	0.005–>200.0	0.4
Clostridium tetani	0.2 – 0.7	0.6
Corynebacterium diphtheriae	0.003– 3.12	1.6
Neisseria gonorrhoeae	0.004– 6.2	1.0
Neisseria meningitidis	0.19 – 6.2	3.12
Haemophilus influenzae	0.1 – 20.0	3.1
Hemophilus pertussis	0.1 – 6.2	0.2
Brucella	0.3 – 10.0	5.0
Escherichia coli	12.5 – 100.0	100.0
Aerobacter aerogenes	62.5 –>200.0	200.0
Klebsiella pneumoniae	3.12 –>200.0	>200.0
Pseudomonas	125.0 –>200.0	>200.0
Proteus	250.0 – 250.0	250.0
Salmonella	12.5 –>200.0	>200.0
Shigella	25.0 – 100.0	100.0

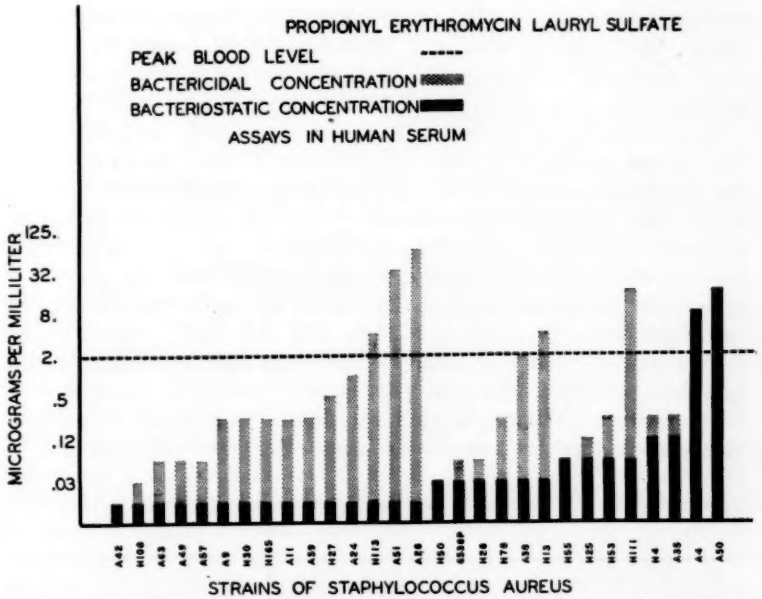

Fig. 14. Twenty coagulase-positive *Staphylococcus aureus* strains were obtained from patients outside the hospital. These were all proved sensitive to penicillin and then were tested with erythromycin for bacteriostatic and bactericidal endpoints in human serum. The average serum concentration reached in 10 subjects was 2 mcg./ml. From the above it is obvious that erythromycin is bactericidal against the majority of erythromycin-sensitive strains of staphylococci.

Clinically, erythromycin achieves serum concentrations that are bactericidal against hemolytic streptococci and pneumococci. Erythromycin-sensitive staphylococci are killed by concentrations that can be obtained with therapeutic doses of erythromycin. Like penicillin, erythromycin has only a bacteriostatic effect on the more resistant strains (Fig. 14).

MODE OF ACTION

Erythromycin exerts its effect on multiplying organisms in a way that suggests it interferes with the metabolic processes of bacteria. Protein synthesis is interrupted without particularly affecting synthesis of nucleic acids.[10] Some interference in the pathway of intermediary carbohydrate metabolism also may occur.

PHARMACOLOGY

Erythromycin base is partially destroyed by stomach acid after oral administration. Most of that which passes into the intestine is absorbed into the blood stream, from which it diffuses readily into the body fluids.[35] Animal studies have shown high tissue concentration in the muscle, skin, viscera, heart and other organs. All tissues except the brain have higher concentrations than the serum, and these are retained long after the blood levels have disappeared (Table 25).[57]

Erythromycin base and its salts are not consistently absorbed after oral administration to human test subjects. This is in contrast with the reproducible, higher and more persistent concentrations obtained with the propionyl erythromycin[12, 69, 72, 103] and erythromycin estolate.[28, 43]

Food reduces the absorption of erythromycin and its salts, but erythromycin estolate may even have increased absorption when given with food.[28]

Erythromycin does not readily diffuse across the normal meninges into the cerebrospinal fluid. In patients with meningitis, assayable concentrations are obtained. Erythromycin has been reported to be clinically effective against meningococci resistant to other antibiotics.[1]

TABLE 25. *Tissue Distribution of Propionyl Erythromycin Lauryl Sulfate, mcg./Gm.*

	2 HOURS	7 HOURS
Serum	0.68	0.41
Liver	4.43	2.89
Spleen	4.30	3.29
Kidneys	3.07	1.91
Lung	5.79	5.53
Heart	3.34	1.55
Brain	0.20	0.17

Approximately 2 to 5 per cent of orally administered erythromycin preparations is excreted in the urine,[27] whereas 12 to 15 per cent is excreted by this route after intravenous erythromycin glucoheptonate.[25]

Erythromycin traverses the placental barrier, producing levels in the fetal circulation that are 6 to 20 per cent of the maternal value.[17, 35, 50]

TOXICITY

Toxicity of erythromycin for mice is shown in Table 26. Tests in the rat, the rabbit and the dog confirm the low order of toxicity in mice. Daily doses of approximately 40 mg. per kilogram in the diet of rats and 220 mg. of erythromycin estolate per kilogram given orally daily to dogs for 3 to 6 months did not alter their weight or cause alteration in blood cell counts or abnormalities in the viscera. Eighth nerve damage did not occur in cats given 50 mg. per kilogram intramuscularly for 2½ months.[3]

Toxic amounts of erythromycin in man apparently have never been recorded, possibly because gastrointestinal side effects limit high oral dosage. In a study of possible effectiveness of erythromycin in the treatment of tuberculosis, blood levels of 20 to 40 micrograms per cubic centimeter were obtained in 3 patients taking 8.0 gm. orally daily for 3 to 5 months with no evidence of toxicity.[26] Doses of 7.0 to 8.0 gm. of erythromycin glucoheptonate have been given intravenously daily with no toxicity noted.[75]

Johnson and Hurst[46] gave 2.75 gm. intravenously for 12 days to a 3-year-old child with no signs of toxicity. Doses greater than 20 mg. per pound per day orally in children may be accompanied by signs of gastrointestinal irritation, including nausea, vomiting and diarrhea.

Intrahepatic cholestatic type of jaundice has occurred in seven patients taking erythromycin estolate. Abdominal cramping with nausea or vomiting, or both, occurred after 10 to 14 days of oral administration. These symptoms were followed by jaundice, fever, leukocytosis and eosinophilia. Elevated serum bilirubin and transaminase values were associated with low or weakly positive cephalin flocculation and thymol turbidity tests. Cholecystograms were negative, symptoms subsided, and results of laboratory tests returned to normal within two to three days after stopping the antibiotic. In four of the seven patients a repeat course of therapy caused a return of symptoms, fever, and

TABLE 26. *Toxicity of Erythromycin for Mice*

	LD_{50}	
	ERYTHROMYCIN BASE	PELS
Oral	3.0 gm./kg.	6.4 gm./kg.
Intravenous	0.4 gm./kg.	

laboratory findings. One of these four had a liver biopsy performed during the second episode. This showed a periportal infiltration of lymphocytes, a few polymorphonuclear leukocytes and many eosinophils, and was interpreted as intrahepatic cholestasis.

There are incomplete reports on six additional patients with recurrence of jaundice on a second course of erythromycin estolate. Three instances of elevated transaminase levels without jaundice have been noted in patients with nausea and abdominal cramping.

The history of a sensitization time interval and the association with eosinophilia both peripherally and in the liver biopsy suggest there may be a hypersensitivity to erythromycin estolate in some patients, manifested by an intrahepatic cholestatic type of jaundice.

Even though reports have been infrequent, the recurrence of jaundice with repeated challenge establishes this as a definite entity.

Hall[7] has suggested that patients with decreased liver function should receive propionyl erythromycin cautiously. This recommendation probably should also be made about its use in patients known to be allergic or hypersensitive to other medications.

Kuder[54] reported an incidence of 2.5 per cent side effects with erythromycin estolate in a study including 10,377 children under age 16. Herrell[40] considered erythromycin to be the least toxic of the antibiotics generally prescribed.

CLINICAL STUDIES

Streptococcal Infections

Extensive experience with erythromycin in streptococcal infections has established its effectiveness. Finland et al.[20] studied the susceptibility of beta hemolytic streptococci to 11 antibiotics in vitro. The most active antibiotics against the 394 strains tested were penicillin and erythromycin.

Patients with acute follicular tonsillitis due to *Streptococcus pyogenes* have shown rapid clinical improvement when given erythromycin.[11, 29, 30, 35, 42, 92] Frequently the causative organism could not be cultured after 12 hours' treatment. A similar result is usually obtained in acute streptococcal pharyngitis.[29, 35] The fever quickly subsides, and there is a prompt decrease in local edema and pain.

In scarlet fever, erythromycin has produced dramatic clinical improvement.[30] The skin rash runs a course only slightly shorter than normal, but all other signs of active infection usually disappear within two to five days. Haight[31] confirmed these results in a controlled series involving 208 patients with scarlet fever. Seventy-eight of the patients were treated with erythromycin, 78 were given procaine penicillin, and

52 received placebos. No significant differences were found between the therapeutic efficacy of oral erythromycin and that of intramuscular procaine penicillin. Both antibiotics suppressed the formation of antistreptolysin O. Erythromycin was also equally effective as penicillin in preventing the suppurative complications that frequently follow this disease.

The American Heart Association recommends that effective antibiotic blood levels be maintained for a minimum of 10 days in an effort to prevent rheumatic fever by eradication of the streptococci.

For prophylactic use in patients with a history of rheumatic fever or congenital heart disease, penicillin has been recommended as the antibiotic of choice. Erythromycin also has been demonstrated to be an effective agent for such use.[85] Tidwell and Lewis[93] have published the results of a four-year study of erythromycin used prophylactically against group A streptococcal infections. They concluded that erythromycin was a satisfactory substitute for penicillin as a prophylactic agent. Of interest, they noted no change in the pattern of antibiotic sensitivity of staphylococci cultured from the families involved.

Soft-tissue infections, cellulitis, and erysipelas due to *Streptococcus pyogenes* have improved rapidly under erythromycin therapy. Satisfactory results have also been obtained in the treatment of osteomyelitis and subacute bacterial endocarditis due to streptococcal organisms.[29, 35]

Clinical evidence has suggested that the presence of penicillinase-producing staphylococci in the nasopharynx may be responsible for decreasing the effectiveness of penicillin in acute streptococcal pharyngitis. Erythromycin administered along with penicillin in such cases has eradicated both the staphylococci and hemolytic streptococci.[16]

When drugs other than penicillin are used, it is important to give erythromycin preparations in streptococcal infections,[61, 100] since broad-spectrum drugs are not effective in eradicating the organisms from the pharynx, and relapse of pharyngitis may occur. In addition, strains of group A streptococci have been encountered which have developed resistance to broad-spectrum drugs.[55, 60]

Pneumococcal Infections

Most strains of *Diplococcus pneumoniae* are sensitive to the action of erythromycin preparations, and these medications have been used extensively in the treatment of pneumococcal pneumonia.[29, 30, 52, 81, 82, 89, 99]

Calesnick[11] and Settel[80] have also reported cases of pneumococcal pneumonia which responded satisfactorily to the propionyl erythromycin ester. Reichelderfer et al.[73] treated pneumococcal pneumonia in children with various dosages of erythromycin estolate. One patient

recovered satisfactorily on a dosage of 20 mg. per pound per day. Of 7 children treated with one-fourth this dosage (only 5 mg. per pound per day), 5 improved or recovered satisfactorily. Two of the latter demonstrated a mixed infection with organisms less sensitive than *Diplococcus pneumoniae—Hemophilus influenzae* in one and *Staphylococcus aureus* in another.

Romansky et al.[76] reported more than 100 cases and Haviland[34] 60 cases of pneumonia treated with erythromycin. Both observed results similar to those obtained with penicillin. After reviewing the clinical reports of pneumococcal pneumonia Herrell[39] concluded that erythromycin compares favorably with penicillin. Austrian[4] considered erythromycin to be generally as efficient as penicillin in the treatment of pneumococcal pneumonia.

Staphylococcal Infections

Erythromycin preparations have been used successfully in the treatment of a wide variety of staphylococcal infections, including pharyngitis, furunculosis, pyoderma, septicemia, urinary tract infections, postoperative empyema, wound infections and ileocolitis.

Hirsch, Kunin and Finland[42] compared the antistaphylococcal activity of the serum of persons given single doses of propionyl erythromycin. After a single 500-mg. dose of propionyl erythromycin the peak level of serum activity was obtained at 2 hours (the patient's serum could be diluted an average of 32 times and still inhibit the staphylococcus) and antistaphylococcal activity was still present at 12 hours.

Smith and Soderstrom[82] concluded that propionyl erythromycin was particularly useful in the treatment of staphylococcal disease. Their 74 cases included patients with acne, furuncles, carbuncles, infected stasis ulcers, pyodermas, pharyngitis, osteomyelitis and pneumonia.

Particular note should be made of the important role that erythromycin plays in the treatment of staphylococcal enterocolitis, both when it arises spontaneously and when it results from therapy with other antibiotics to which the staphylococci have become resistant.[14, 23, 68, 95] This enteritis has also been observed when certain antibiotics have been used to sterilize the intestinal tract before operation. The clinical picture may appear from the first to the fourth postoperative day and is characterized by nausea, vomiting and a few loose stools. Next, profuse diarrhea usually develops and leads to a severe shocklike state. An overwhelming number of staphylococci appear in the smear, or a pure culture can be isolated from the stools. They frequently are more sensitive to erythromycin than to other antibiotics in common use. Newman[66] and Pettet et al.[70] have emphasized that diarrhea is not necessarily

present in all cases. Other investigators have shown that erythromycin therapy may be lifesaving in the treatment of staphylococcal enterocolitis.[15, 95]

For staphylococcal infections that are slow to respond to therapy, such as endocarditis, osteomyelitis, meningitis and pyelonephritis, combinations of antibiotics are used in most instances. In addition, parenteral therapy may be indicated. Erythromycin may be administered parenterally in the form of erythromycin glucoheptonate, followed by oral therapy when this becomes feasible. Erythromycin in combination with streptomycin, bacitracin, chloramphenicol and other drugs has been useful in such cases.[39, 81, 83]

Erythromycin has been shown by Herrell[41] to be highly effective in vitro and in staphylococcal infections when used in combination with penicillin V. From his preliminary studies Dr. Herrell indicates that this is the most effective combination of antibiotics available at present for the oral therapy of staphylococcal infections due to antibiotic-resistant staphylococci.

Staphylococcal pneumonia in infants and children presents difficult problems in management. Antibiotic therapy should consist of combinations of drugs in adequate doses. Erythromycin has been effective in such patients.[13, 36, 45, 53, 71, 77] Reichelderfer et al.[73] found erythromycin estolate effective in five out of six cases of staphylococcal pneumonia in children.

Hemophilus Infections

Love and Finland[59] have shown that strains of *Hemophilus influenzae* are generally sensitive to erythromycin in concentrations of 0.5 to 3.0 micrograms per milliliter and have considered that the activity of erythromycin in vitro against these bacteria is similar to that of oxytetracycline. Zinnemann[103] found *Hemophilus influenzae* strains highly sensitive, with few exceptions, to comparatively low concentrations of erythromycin. Pneumonia caused by *Hemophilus influenzae* has responded rapidly to erythromycin therapy.[79, 94] Nasou et al.[65] used erythromycin successfully in the treatment of a patient with *Hemophilus influenzae* pneumonia complicated by bacteremia, and Romansky et al.[75] reported that satisfactory responses were obtained in patients with *Hemophilus influenzae* meningitis and otitis media.

Pertussis

Though erythromycin has been shown to be more effective in vitro against this organism than other antibiotics, including chloramphenicol,

it has had only limited use clinically.[9] Most investigators conclude that once the paroxysmal stage is reached, the clinical course is not noticeably changed by antibiotics other than preventing or eliminating a superinfection bronchopneumonia.

Diphtheria and Diphtheria Carriers

Early studies in vitro indicated that diphtheria organisms are among the most sensitive to the action of erythromycin.

In the Osaka Momoyama Isolation Hospital in Japan,[102] 13 patients with diphtheria were treated with erythromycin. Ten of the 13 patients received no diphtheria antitoxin at any time during therapy. In every case a favorable response to the antibiotic could be seen within 24 hours. No relapses occurred.

Blake[6] concluded that erythromycin is the most potent antibiotic for the treatment of diphtheria. But antibiotics will not neutralize the previously elaborated toxin of *Corynebacterium diphtheriae*, and it is recommended that diphtheria antitoxin be combined with erythromycin therapy in the care of acutely ill patients.

Beach and co-workers[5] used erythromycin in conjunction with diphtheria antitoxin in the treatment of 43 patients with diphtheria. In this study, erythromycin eradicated the *Corynebacterium diphtheriae* from the nose and throat in all cases in an average time of two days.

Forbes[21] administered a 5-day course of erythromycin to 14 patients with diphtheritic infections. The bacteria had persisted through two courses of penicillin therapy. All responded to erythromycin. No virulent organisms were demonstrable four days after cessation of treatment.

Haight and Finland[30] administered erythromycin to three carriers of virulent diphtheria bacilli who had persistently shown positive cultures during penicillin therapy. In each case at least three negative cultures were obtained at intervals of one to three days after the end of therapy. Blute[8] and Ricci et al.[74] have also used erythromycin successfully in the management of the diphtheria carrier state.

Kempe concluded that erythromycin "is the agent of choice in the treatment of patients with diphtheria or of diphtheria carriers."[51]

Additional Clinical Infections

Erythromycin, because its spectrum is more extensive than that of penicillin, has been tried in clinical infections other than those discussed above. Erythromycin has been shown to be effective in amebiasis.[2, 19, 67, 86, 98] It can be used for the treatment of syphilis in those patients who cannot be given penicillin.[62–64, 91]

TABLE 27. *Dosage Schedules of Erythromycin*

CHILDREN—ORALLY	
10-25 pounds	20 mg./lb./day*
25-50 pounds	125 mg. every 6 hours
Over 50 pounds	250 mg. every 6 hours
ADULTS—ORALLY	
Usual dose	250 mg. every 6 hours
Severe infection	500 mg. every 6 hours
Overwhelming infection	0.5–1.0 gm. every 6 hours, parenterally

* For more severe infections, 30 to 40 mg./lb./day in divided doses may be needed. In overwhelming infections the dosage recommended for oral use can be given parenterally.

We usually administer antibiotics every 6 hours until the infection is controlled, and then shift to a more convenient "with meals and bedtime" (q.i.d.) schedule.

Tetanus bacilli have also been eradicated early in the course of therapy of tetanus, possibly because this organism is usually more sensitive to erythromycin than to any other antibiotic.[26, 49, 97] It is recommended that it be used in conjunction with antitoxin, since the antibiotic has no effect on the tetanus toxin already circulating in the patient's tissues. Herrell[38] used erythromycin successfully in the treatment of actinomycosis.[38] Ninety-six per cent of the cases of gonorrheal urethritis responded to 2.0 gm. of erythromycin in single divided dosage.[24] Others have also reported successful erythromycin therapy of gonorrhea.[29, 30, 32, 56, 84] Brucellosis has responded to erythromycin, particularly the melitensis variety.[33, 58, 96]

The dosage schedules recommended for the erythromycin preparations are shown in Table 27, and the preparations available for systemic therapy are listed in Table 28.

SUMMARY

Erythromycin has a fairly wide antibacterial spectrum, including the gram-positive cocci and bacilli. It has been shown to be effective against both streptococcal and pneumococcal infections involving the upper and lower portions of the respiratory tract. There is no cross resistance with other antibiotics, except for the less effective erythromycin-like antibiotics, carbomycin, spiramycin and oleandomycin. Erythromycin is well tolerated after oral administration and can be combined with other antibiotics with no evidence of antagonism. Enhanced action has been demonstrated against staphylococci when used in combination with the other antibiotics, particularly penicillin.

TABLE 28. *Preparations of Erythromycin for Systemic Use*

FORMS	CONCENTRATION OR SIZE	MANUFACTURER	TRADE NAME	COMMENTS
Oral:				
Tablets	100 mg., 250 mg.	Abbott	Erythrocin	Film-coated stearate salt
Suspension	200 mg./5 cc.	Abbott	Erythrocin	Ethyl succinate, pediatric
Capsules	125 mg., 250 mg.	Lilly	Ilosone	Erythromycin estolate
Suspension	125 mg./5 cc.	Lilly	Ilosone	Erythromycin estolate
Drops	100 mg./cc.	Lilly	Ilosone	Erythromycin estolate
Tablets	100 mg., 250 mg.	Lilly	Ilotycin	Acid-resistant coating, erythromycin base
Suspension	200 mg./5 cc.	Lilly	Ilotycin	Ethyl carbonate, pediatric
Drops	100 mg./cc.	Lilly	Ilotycin	Ethyl carbonate
Parenteral:				
Dry Powder	300 mg./10-cc. vial	Abbott	Erythrocin I.V.	Lactobionate salt
	1 gm./30-cc. vial	Abbott	Erythrocin I.V.	Lactobionate salt
Solution	50 mg./cc. in 2-cc. and 10-cc. vials	Abbott	Erythrocin I.M.	Ethyl succinate, intramuscular
Dry Powder	250 mg./20-cc. vial	Lilly	Ilotycin I.V.	Glucoheptonate salt
	500 mg./30-cc. vial	Lilly	Ilotycin I.V.	Glucoheptonate salt
	1 gm./50-cc. vial	Lilly	Ilotycin I.V.	Glucoheptonate salt

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OLEANDOMYCIN AND TRIACETYLOLEANDOMYCIN

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Oleandomycin is an antibiotic elaborated by a strain of *Streptomyces antibioticus* when grown in appropriate environmental conditions. It was first described by Sobin et al.[33] Celmer et al.[6] prepared and described several oleandomycin derivatives in 1957. Of these, triacetyloleandomycin proved to be pharmacologically superior to oleandomycin by providing higher serum concentrations and a lower ED_{50}. Triacetyloleandomycin provides the same antibacterial activity in vivo as oleandomycin as a result of deacetylations and the formation of oleandomycin. Hence the clinical activity of these two agents may be regarded as one. These findings plus the improved absorption in man indicate a superior oral preparation over previous oleandomycin forms.

PHYSICAL PROPERTIES

Oleandomycin as the hydrated crystalline hydrochloride salt is a weak base and appears as a colorless needle. Oleandomycin base has a lower degree of solubility (0.5 gm. per 100 ml. of water). Oleandomycin is highly soluble in alkaline aqueous solutions and organic solvents.

Triacetyloleandomycin is poorly soluble in water (less than 0.1 gm. per 100 ml. of water), as well as in buffered aqueous solutions at pH ranges of 4 to 7. It is a stable compound; no loss of potency was noted when aqueous solutions were kept at temperatures of 25° and 37° C. at pH 2.5.

ANTIMICROBIAL ACTIVITY

The antimicrobial activity of triacetyloleandomycin is effected in vivo by deacetylation and provision of oleandomycin; hence the spectrums of

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TABLE 29. *Susceptibility of Bacteria to Oleandomycin—Ranges of Inhibitory Concentrations* MCG. / ML.

Streptococcus:	
Pyogenes	0.05 – 3.12
Faecalis	0.312– 3.1
Viridans	0.14 – 2.25
D. pneumoniae	0.01 – 3.90
Staphylococcus aureus	0.16 –>100
C. diphtheriae	0.039– 1.56
L. monocytogenes	0.78 – 3.12
Ery. rhusiopathiae	0.19 – 0.7
Bacillus:	
Subtilis	0.39– 1.7
Anthracis	0.48 – 5.0
Mycoides	1.56
Clostridia species	1.50 – 7.00
Neisseria:	
Gonorrhoeae	3.12 – 6.25
Meningitidis	1.56 – 6.25
Brucella species	0.4 – 6.25
Hemophilus:	
Influenzae	0.078–20.0
Pertussis	0.2
K. pneumoniae	25–>100
A. aerogenes	>100
E. coli	>100
Ps. aeruginosa	>100
Salmonella species	50–>100
Shigella species	>100

Ranges of minimum inhibitory concentrations compiled from 8 laboratories.

activity for the two preparations are considered identical. Sobin et al.[33] described the antibacterial spectrum for oleandomycin in 1954. They demonstrated activity against many gram-positive bacteria, including streptococci, pneumococci, staphylococci, large aerobic spore-forming bacilli, anaerobic clostridia, corynebacteria, *Listeria monocytogenes* and *Erysipelothrix rhusiopathiae*. The gram-negative spectrum is limited to the genera of *Hemophilus, Brucella,* and *Neisseria.* Most gram-negative organisms, however, are not affected by oleandomycin. The susceptibility in vitro of microorganisms to oleandomycin is shown in Table 29.

English and McBride[7] described the antimicrobial activity of triacetyloleandomycin. Activity in vitro of triacetyloleandomycin was less than that of the oleandomycin base. Seven strains of resistant staphylococci were found to require two to four times the amount of triacetyloleandomycin as the oleandomycin base for minimum inhibitory concentrations. Mouse-protection tests in vivo against experimental staphylococcal infections demonstrated ED_{50} ranges from 36 to 105 mg. per kilogram.

CROSS-RESISTANCE WITH ERYTHROMYCIN

Since oleandomycin is a member of the macrolide group of antibiotics

and has an antimicrobial spectrum similar to erythromycin, it is not surprising that cross-resistance between these two antibiotics has been noted.

Sobin et al.[33] and Fust et al.[11] found cross-resistance to laboratory-developed erythromycin-resistant strains of staphylococci.

Garrod[13] confirmed later that resistance which occurred in vitro uniformly appeared for both erythromycin and oleandomycin. He also noted that erythromycin-resistant strains isolated from patients may or may not show this cross-resistance. The clinical significance of this dissociated resistance is not clear. It would be well to keep in mind the fact of possible cross-resistance when selecting therapy for erythromycin-resistant staphylococcal infections, since development of oleandomycin resistance might be anticipated, and vice versa.

PHARMACOLOGY

In an extensive study by Bernstein and Piller[3] peak serum concentrations following a 250-mg. oral dose of oleandomycin in 10 subjects averaged 2.9 micrograms per milliliter 3 hours after administration. In this same group which received multiple doses (250 mg. every 4 hours), 4 of the 10 subjects failed to achieve levels of 2 micrograms per milliliter. In a series of 7 patients given 0.5 gm. orally every 4 hours, serum concentrations ranged from 2.0 micrograms per milliliter to a high of 16.5 micrograms, suggesting some cumulative effect following multiple doses.

Oleandomycin is suitable for intravenous administration. Serum concentrations after rapid intravenous administration of 250- to 500-mg. doses decline in the first 10 minutes and drop in 4 to 6 hours to less than 1 microgram per milliliter.[3] Slow intravenous infusions of 1 to 2 gm. per day occasionally produced concentrations in excess of 2 micrograms per milliliter, but generally 1 microgram per milliliter or less was observed. After a single intravenous dose of 250 mg., only 18 per cent was recovered in the urine within 4 to 6 hours.

Intramuscularly, oleandomycin in adults did not result in concentrations that might be considered significant clinically.[21] Asay and Koch[2] gave 12.5 to 25 micrograms per milliliter to children with resultant concentrations adequate for antibacterial activity, but the larger doses were no more effective in producing serum concentrations than the smaller doses. Parenteral administrations have been accompanied by pain in some instances.

Shubin et al.[31] showed greater serum activity in 30 patients after oral administration of triacetyloleandomycin than that obtained after oral doses of oleandomycin base. Measurable antibacterial activity in serums was observed as long as 12 hours after a single 500-mg. dose. There was also some cumulative activity demonstrable after 24 hours with a dosage schedule of 250 mg. every 8 hours. From 3 to 12 per cent of orally administered doses of oleandomycin was recovered in the urine

in a 24-hour period, compared to 18 to 24 per cent for triacetyloleandomycin, in the same subjects, reflecting better absorption of triacetyloleandomycin.

Triacetyloleandomycin is not suitable for parenteral injection because of its low solubility, and has not been available for parenteral studies.

Extensive studies on tissue distribution of oleandomycin in animals are available, but lacking for man; however, animal studies including primates have shown high concentrations in the kidney, pancreas, spleen, and liver and lung.[17] No significant concentrations were found in the brain. Highest concentrations were found in the liver in rats and dogs.

Studies by Spitzy and Hitzenberger[36] indicate a high degree of distribution throughout intracellular and extracellular fluids of man.

Measurable amounts were found in the cerebrospinal fluid after oral and parenteral administration. With 500-mg. oral doses, concentrations ranged from less than 0.2 microgram per milliliter to a high of 1.4 micrograms per milliliter.[3] These concentrations represented 10 per cent or less of those in serums obtained at the same time. One-hour cerebrospinal fluid concentrations of 2.5 to 5.0 micrograms per milliliter were reported[9] in pediatric patients without meningitis after parenteral injections; corresponding serum concentrations by serial dilution tests were 2 to 4 times greater. Six-hour levels were in the range of 1.2 to 2.5 micrograms per milliliter. Slow intravenous infusions give lower cerebrospinal fluid levels.[19]

Biliary excretion studies showed concentrations ranging from 182 (B bile) to 257 micrograms (A bile) per milliliter 4 hours after administration of a 500-mg. oral dose.[9]

TOXICITY

Oleandomycin has a low order of toxicity. The LD_{50} for rats has been reported as 10,000 mg. per kilogram for subcutaneous and oral routes and 400 mg. per kilogram intravenously. In dogs the LD_{50} by the intravenous route was 300 mg. per kilogram. In chronic administration studies of large doses in rats, no toxic changes were observed in bone marrow, liver, kidney, adrenals, testes, lungs, spleen, heart, thymus or pancreas.[11] Tissue irritation has been noted after subcutaneous injections of 5 and 10 per cent solutions of oleandomycin hydrochloride over a 5-day period.[34]

P'an et al.[26] gave the LD_{50} of triacetyloleandomycin for mice at 198 mg. per kilogram and for rats, 117 mg. per kilogram. Doses as high as 500 mg. per kilogram were tolerated orally. Rats and monkeys showed fatty metamorphosis of the liver after prolonged administration of triacetyloleandomycin at high levels. This was reversible within two weeks after

discontinuation of the drug. Dogs showed no liver changes at 250 mg. per kilogram, but larger doses caused emesis.

Toxic symptoms when produced by large dosages have been depression, ataxia, pilomotor reactions, convulsions and respiratory depression.

Oleandomycin and triacetyloleandomycin have low toxicity in man. Untoward reactions to the use of these agents have been chiefly confined to the gastrointestinal tract. In a previous review by the author[39] 14 studies representing a total of 1136 patients were noted to report an incidence of 3 per cent undesirable reactions. These included nausea, vomiting, diarrhea, esophagitis and nonspecific gastrointestinal complaints. An unaccountable diuresis occurred in 12 patients described by Essellier and Keith.[9]

PEDIATRIC USE—CLINICAL STUDIES

At the time of introduction of oleandomycin and of its early clinical trials, the initial susceptibility-test data and pharmacologic data suggested that oleandomycin would be somewhat less effective than erythromycin. Unfortunately before a proper perspective of its clinical effectiveness could be established, attention was focused on combination therapy, and a fixed combination of tetracycline with oleandomycin was promoted as superior to the single agent in certain clinical situations. Therefore it is not surprising to find a limited pediatric literature on oleandomycin alone. A modest acceptance of triacetyloleandomycin in the past few years has given indication of the effectiveness of this agent in a wide variety of infections. It will be this recent literature—and primarily that of the pediatric literature—which the reviewer will include.

Ross[30] reported in 1955 on the pediatric effectiveness of oleandomycin. Twenty children with pneumonia considered to be of bacterial origin responded within 24 to 96 hours, as evidenced by return of temperature to normal levels; 14 were regarded as good results and 6 as fair responses. Six patients had bacteriologic identification of the causative organisms as *D. pneumoniae*, while one had *H. influenzae*, type B. Therapy consisted of 40 mg. per kilogram of body weight, daily, in 6-hourly doses for 5 to 7 days.

Results in 13 children with diarrhea accompanied by isolation of *Staphylococcus aureus* in the stool showed improvement in one to 4 days of therapy. Subsequent cultures of stools after recovery did not show staphylococci. Ross was cautious to interpret these results as evidence of successfully treated staphylococcal enteritis. Two other patients with Salmonella enteritis and nine children with Shigella dysentery were considered therapeutic failures with oleandomycin therapy.

More recent studies with triacetyloleandomycin have established the

usefulness of this agent in bacterial pneumonia. Isenberg and Karelitz[16] reported 12 cases of pneumonia, of which 2 were associated with *D. pneumoniae* and 10 with staphylococci; a Klebsiella was also isolated from the pharynx of one of the patients with *Staphylococcus aureus*. The recoveries of these children, who ranged up to 15 years of age, were prompt and satisfactory in all but one. Mellman et al.[22] reported 11 young patients with pneumonia principally of gram-positive bacterial origin in whom response was gratifying in 9; one patient with *H. influenzae* predominating in the nasopharynx showed persistence of this organism after 7 days of therapy.

Similarly good results were obtained in staphylococcal and streptococcal pneumonias in 38 children by Koch and Asay.[18] Additional pneumonias which were treated with oleandomycin or triacetyloleandomycin are found in the reports of Wennersten,[37] Werthamer et al.,[38] Ozyazici et al.,[25] McClellan[20] and Newsome.[24]

Most of these authors also describe the usefulness of either of the agents in the management of either upper or lower respiratory tract infections; some of these such as "strep throats" and "tonsillitis" may have had primary bacteriologic etiologies, but many of the bacterial isolates probably represent oropharyngeal flora in the presence of viral infections. Clearing of pathogenic organisms in a wide variety of upper respiratory tract infections after treatment was observed by many authors, but others have simply noted clinical improvement without bacteriologic studies. The pediatrician is referred to the foregoing references to draw his own conclusions as to the role of triacetyloleandomycin in bringing about recoveries.

Otitis media has been successfully managed by the use of triacetyloleandomycin. At least 75 pediatric patients are reported by various clinicians[16, 18, 20, 22, 24, 25, 29, 37] with a cure or good response rate of approximately 95 per cent. Sinusitis in children has also been reported as responding to triacetyloleandomycin.

The role of oleandomycin and triacetyloleandomycin in staphylococcal infections has been reviewed in recent years.[39] Some of the acute bacterial pneumonias included in the pediatric group of patients in this report[18, 22, 25] were associated with pure cultures of *Staphylococcus aureus*, and adequate responses were obtained in most of these patients.

The usefulness of triacetyloleandomycin in staphylococcal soft tissue infections has also been demonstrated by many in the past few years.[16, 18, 20, 22, 24, 25, 29, 37, 38] Chronic furunculosis, abscesses, wound infections, cellulitis and impetigo have been reported to respond with uniformly good results. It is wise to retain a critical attitude that other supportive measures such as skin hygiene, incision and drainage may have contributed as much to the over-all results as the antibiotic therapy.

Isenberg and Karelitz[16] reported clearing of an epidemic strain of

staphylococcus, phage type 80/81, in 7 carriers among obstetrical and pediatric personnel during an outbreak of pyoderma, conjunctivitis and ophthalmitis in a newborn nursery. They gave a dose of 2 gm. of triacetyloleandomycin daily for 4 days. These authors also treated 39 infants and children with pneumococcal, streptococcal and staphylococcal infections with good results in 29 of the series. They used a dosage schedule of 40 mg. per kilogram per day of triacetyloleandomycin in 4 divided doses.

The use of triacetyloleandomycin in the management of pediatric septicemias and bacteremias has been limited.[10, 18, 25] The reports do not indicate that the drug has usually been successful, and improvement rather than cure has been the usual response. One patient with subacute bacterial endocarditis was included in the series of Koch and Asay;[18] this patient was not cured by triacetyloleandomycin. Such results do not encourage additional clinical trials in these serious infections.

Triacetyloleandomycin has been studied as a prophylactic agent in the prevention of streptococcal infections in rheumatic heart disease patients.[4, 5, 23] Breese and co-workers[5] compared the effectiveness of penicillin G, erythromycin and triacetyloleandomycin in the treatment of beta hemolytic streptococcal infections in children. These workers concluded, on the basis of their specified criteria for treatment failure, that triacetyloleandomycin gave effectiveness comparable to that of penicillin G, and slightly better results than erythromycin. They point out, however, that no significant differences were noted between any of these preparations in the group in which the initial organisms cultured and the post-treatment infecting organism could be typed. These authors used a weight-determined dosage schedule: under 50 pounds, 500 mg. in divided doses of 125 mg., 125 mg., and 250 mg. at 8 a.m., 2 p.m. and 8 p.m.; 50 to 100 pounds, 750 mg. total daily dose in 3 divided doses of 250 mg.; 100 pounds and more, 1 gm. total daily dose in 3 divided doses of 250 mg., 250 mg., and 500 mg. Mou's[23] patients ranged from 5 to 69 years of age; he noted suppression of streptococcal infections equal to that by penicillin and recommended it especially for those patients with hypersensitivity to penicillin.

Good to excellent responses were noted in the management of osteomyelitis.[18, 22]

Patients who were treated for presumably staphylococcal enteritis were also noted to have responded well to triacetyloleandomycin,[20, 22, 37] but large-scale trials, and especially in postsurgical patients, are needed to establish the usefulness in this field.

A variety of genitourinary infections have been reported in the therapeutic trials;[18, 22, 37] results in this group of clinical infections have not been uniformly successful because of the large number of gram-negative organisms or mixed infections encountered in this area. Other

reports dealing with combined sulfonamide therapy or other antibiotics in this therapeutic area will not be reviewed here.

In general, oleandomycin and triacetyloleandomycin were well tolerated by the patients. Occasional patients had nausea, vomiting or loose stools. Jaundice was reported developing concurrently with triacetyloleandomycin therapy in three patients by Koch and Asay;[18] the jaundice disappeared within three days of stopping the antibiotic. Isenberg and Karelitz[16] also reported jaundice and hepatomegaly in one patient with laboratory incidence of acute hepatitis; the jaundice and hepatomegaly decreased within two weeks of discontinuation of the drug. Whether these cases were true drug toxicity cannot be established with certainty.

SUMMARY

Oleandomycin and triacetyloleandomycin are macrolide antibiotics effective clinically in a variety of infections primarily associated with gram-positive cocci. Triacetyloleandomycin, which is pharmacologically superior, appears to be effective in a variety of staphylococcal infections. It has been used successfully in the prophylaxis of streptococcal infections. These antibiotics would appear to be secondary to the various penicillins, and perhaps to erythromycin in certain circumstances, but their usefulness in patients with hypersensitivity to penicillin is reassuring to the clinician in the management of gram-positive coccal infections.

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ANTIMICROBIAL THERAPY IN THE NEWBORN INFANT

A Major Area of Ignorance

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The physician caring for the newly born infant could become a nihilist as he reviews the therapeutic tragedies of the last decade. Yet these tragedies were almost predictable—in general, if not in detail. Clinical pediatrics and the present medical approach to children are based upon the demonstrated fact that the child is not just a little man. Likewise, the infant is not just a little child, for the newly born infant has been demonstrated to differ from more mature members of the human species both biochemically and physiologically. Unfortunately, present knowledge of the differences between immature and more mature human beings does not provide assurance that the differences or the similarities can be predicted. In like manner, the effect of a drug on an infant is not necessarily predictable, for drug absorption, metabolism and disposition require a series of incompletely described and perhaps different biochemical and physiologic steps. Furthermore, the changed or unchanged drug may exert a pharmacologic effect on only partially elucidated and possibly different organ, cell or enzyme function.

The dissimilarity of the newborn infant from the adult has been recognized. The possible effect of the difference on the pharmacologic effect of drugs was also recognized before the therapeutic debacles of

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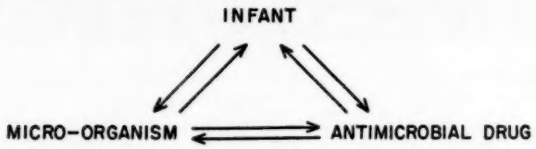

Fig. 15

recent years. This knowledge has not been quickly received by those who sell drugs. Even after recent therapeutic tragedies the newborn infant is not always thought of as a very different organism.

Lack of the recognition of the newborn infant as peculiar with respect to the handling of drugs has provided the reviewers with relatively little upon which to base specific recommendations for the use of antimicrobial drugs in this group of patients. Caution must attend all drug use, and each infant death must be reviewed to determine whether failure resulted from therapeutic omission or commission.

Rational use of an antimicrobial agent in a newborn infant depends upon an understanding of the details of relationship between the patient, the organism and the drug (Fig. 15). Understanding of these details is incomplete.

THE PATIENT AND THE MICROORGANISM

The import of infection during the newborn period is difficult to ascertain. Diagnoses are often in doubt among the living; in autopsy series differences are reported from one locality to another and even from one pathologist to another in the same locality. Despite the uncertainty, however, more or less general agreement exists on the following: (1) newborn infants and particularly premature infants are more susceptible to infection than more mature members of the species; (2) disseminated infection is a frequent primary and a frequent contributing cause of death in newborn infants; and (3) the clinical signs of infection or response to infection are subtle and may be detected only with difficulty, sometimes only when death is imminent.

Infections of the newborn infant have been divided into those acquired (1) before birth, (2) during birth, and (3) after birth.[23] This classification provides basis for logical thought about the infections of newborn infants, although the time of acquisition of infection cannot always be determined, even in retrospect.

Infections acquired before birth are of great concern and probably account for the greatest number of neonatal deaths resulting from infection. The locus of the primary infection is most often the lungs, less frequently the blood, and occasionally the skin. Various therapeutic and diagnostic schemes have resulted from the association of

these infections with premature rupture of maternal membranes, long and difficult labor, premature delivery, septic delivery, or microscopic evidence of placental or cord inflammation. None of these schemes has yet proved satisfactory; however, current intensive research activity in many centers may provide improved methods for selecting the infant for antimicrobial therapy who has significant infection at the time of birth.

At present in the nurseries of the Cincinnati General Hospital diagnostic cultures are obtained on infants who are thought to be candidates for severe infection on the basis of the clinical history of maternal sepsis or prolonged rupture of maternal membranes. A therapeutic course of antimicrobial therapy is begun, sometimes before the results of the cultures are known. This is done with the knowledge that the infecting organisms are most often vaginal or enteric bacteria such as *Escherichia coli*, Paracolobactrum, and streptococci (enteric strains as well as group A). These organisms are not likely to be unusually resistant to antimicrobial drugs unless maternal hospitalization or antimicrobial therapy has preceded delivery.

Infections acquired after birth are a less homogeneous group from the standpoint of etiologic agents than are infections acquired before or during birth. This group of neonatal infections may result from any of a wide variety of organisms acquired from any one of many different sources. Occasionally, these infections are acquired in nurseries with bacterial spread of epidemic proportions. When multiple infants with infection are observed sequentially, asumptions about the etiologic agent and its susceptibility to drugs may be made before obtaining cultural and bacterial drug sensitivity data.

THE MICROORGANISM AND THE DRUG

The effect of drugs on microorganisms has been reviewed extensively. The present authors do not propose to review again at length this aspect of the relation between drugs, infants and microorganisms, although knowledge of this relation is necessary for treatment of the newborn infant with infection or presumed infection. Suffice it to say that the physician caring for the newborn infant need not have an extensive knowledge of every drug or combination of drugs now marketed to treat adequately and intelligently the newborn infant with severe bacterial infection.

THE DRUG AND THE PATIENT

The biochemical and physiologic functions of the patient may potentiate or may decrease the antimicrobial effect of a drug. Similarly, the drug may increase or decrease one or more biochemical or physiologic functions of the patient. As considered above, the summation of these

effects in the infant is not necessarily predictable from information obtained from more mature subjects, either human or nonhuman species.

The relations between *drugs and the infant* and between *the infant and drugs* are least well understood of the various relations touched upon here. This offers additional argument for a more limited antimicrobial regimen when dealing with newborn infants. Exact limits should not be imposed, however, for antimicrobial sensitivity studies may dictate the use of additional drugs in an occasional patient. The physician, however, uses only drugs which are effective and are safe either by his own critical observation and experience or by the critical observation and experience of others. The use of drugs with which the physician has had little experience or use of drugs in new dosages or forms should be cautious and should be preceded by a review of published information providing adequate assurances of safety in newborn infants.

In many instances proof of safety of a drug for the infant is lacking. The limits of safety for the newborn infant and the factors influencing drug safety are known for only a few drugs. It is therefore the authors' hope that the following brief review will not be accepted as the final word, but only as an indication of some areas of knowledge and, by implication, some of the areas of ignorance.

It is obvious that many drugs in common use require intensive reevaluation, and new drugs will require more scrutiny than drugs have received in the past. Perhaps lethal toxicity studies in newborn animals will prove meaningful, though it would not be impossible that they prove misleading from time to time. Determination of dose-response and of drug metabolism, distribution and disposition in fetal and adult animals should be compared. Finally, pharmacologic properties and clinical drug effects must be assessed in the clinical situation.[10]

In the past, lack of study of the effect of drugs in the newborn infant was construed to indicate safety. In the future, ignorance of a drug must not be construed to mean anything but a lack of knowledge of the drug, necessitating cautious clinical application.

THE DRUGS

Antimicrobial drugs have been divided, subdivided and grouped on the basis of numerous differences and similarities. In this discussion the authors elect to divide and group according to the following naive criteria: (1) old-fashioned drugs, (2) broad-spectrum drugs, (3) drugs for the staphylococcus, and (4) drugs for the gram-negative organisms.*

* The reader is referred to the report of Drs. Heinz Eichenwald and Henry Shinefield[13] for a wealth of new data on dose-blood level responses in newborn and premature infants and to the review of Dr. William Nyhan[24] on the general subject of drug toxicity in newborn infants.

Old-Fashioned Antimicrobial Drugs

These were the first drugs of the current antimicrobial era: sulfonamides, penicillin and streptomycin.

Sulfonamides were frequently used in the treatment of proved or presumed neonatal bacterial infection until the report of Silverman and co-workers.[33] They found a significantly higher death rate in premature infants receiving penicillin and Gantrisin (sulfisoxazole) than those receiving oxytetracycline (Terramycin). The difference was most significant in death rates of infants over the age of 72 hours. Furthermore, there was a significantly higher incidence of kernicterus in autopsies performed on infants receiving the penicillin/Gantrisin combination. MacLean and coauthors[21] reported that hyperbilirubinemia did not seem to be the only cause of kernicterus in this group of infants, for some of the infants had kernicterus with serum bilirubin levels below those usually implicated.

Odell[25, 26] furnished an explanation for the production of kernicterus at lower serum bilirubin levels by demonstrating that sulfisoxazole, other sulfonamides, salicylate, hematin, caffeine sodium benzoate, other organic anions, and increased hydrogen ion concentration could uncouple bilirubin from protein molecules and render it diffusable through membranes otherwise impermeable to protein. Presumably the normal partially effective barrier to bilirubin passage into cells of the brain is protein. Kernicterus can occur when this barrier is rendered ineffectual by a displacement of bilirubin from the protein.

Sulfonamides are now seldom used in antibacterial therapy of newborn infants. Occasionally bacterial sensitivity tests indicate that sulfonamides are still the antibacterial drug of choice. In these rare instances care should be taken that the serum bilirubin of the infant is neither elevated nor likely to become elevated. Sulfonamide therapy of the pregnant woman with long-acting preparations is contraindicated after the first half of pregnancy. (See also page 1091.)

Penicillin is frequently utilized in infections in newborn infants because of its effectiveness against a variety of gram-positive organisms, its presumed low toxicity and its bactericidal action. It is readily absorbed after intramuscular or subcutaneous injection, absorption varying with the preparation. Peak blood levels are attained in 15 to 30 minutes after the injection of aqueous penicillin G, therapeutic levels lasting 2 to 4 hours. Only about one fourth of an orally administered dose of penicillin G is absorbed, the remainder being inactivated by the gastric juice and intestinal bacteria. Oral administration of phenoxymethyl penicillin (penicillin V) produces blood levels two to three times as high as those obtained with oral penicillin G.

Penicillin is distributed throughout the body with significant amounts in the blood, liver, bile, skin and intestine, smaller amounts in various body cavities, and very little in brain, nerve or bone marrow.

Very high concentrations are found in the kidney. It does not readily cross the blood-brain barrier unless the meninges are inflamed, when therapeutic levels may be achieved with high intramuscular doses. It does cross the placenta in significant amounts.

In adults 60 to 90 per cent of an intramuscular dose of aqueous penicillin G is excreted in the urine, most within the first hour. Approximately 20 per cent is eliminated by glomerular filtration and 80 per cent by tubular excretion. About 50 per cent of the excreted drug is biologically active, and the remainder is inactivated in tissues by an unknown mechanism. A small amount is excreted in bile and in human milk.

Barnett and co-workers reported that the renal clearances of aqueous penicillin G and procaine penicillin were reduced in newborn and premature infants because of their diminished renal function. Consequently, lower doses and less frequent administration of the drug are needed in newborns to produce therapeutic blood levels. In premature infants the injection of 30,000 units per kilogram of penicillin G produces blood levels of 80 to 140 units per milliliter, detectable levels persisting 24 hours after injection.[13]

Penicillin's low toxicity renders it useful in newborn infants. In adults, doses of 100,000,000 units per day with blood levels of 100 units per milliliter have been given without ill effects,[14] but the report of Bateman and coauthors[2] suggests that there is a limit to the amount of penicillin which can be tolerated by the adult human being, and beyond this limit death may occur. The finding that penicillin is 7.2 times more toxic to the newborn rat than to the adult rat[22] suggests that it may be more toxic to human newborn infants than to adults and that the amount of penicillin which may be safely administered to infants is limited. It is possible that the limit may have been exceeded in infants with septicemia or meningitis who daily received many million units of penicillin. Hypersensitivity reactions to the drug are uncommon in newborn infants.

At the Cincinnati General Hospital penicillin is administered to newborn and premature infants by injection. For the majority of infections, 20,000 to 50,000 units per kilogram of aqueous penicillin is given intramuscularly every 24 hours in divided doses 12 hours apart. Continuous intravenous infusion is reserved for severe infections such as meningitis when a constant high blood level is desired. In infants whose mothers have a positive serology and who have received inadequate treatment, 150,000 units of procaine penicillin is administered daily for 10 days. Sterile abscesses are encountered infrequently. Winick and co-workers[45] found serum levels of 5 units per milliliter in 3 to 4 hours with decreasing levels for 12 hours after the oral administration of penicillin V in doses of 30,000 units per kilogram every

8 hours. On this basis Eichenwald and Shinefield[13] recommended 30,000 units per kilogram of penicillin V orally every 8 hours.

Since the discovery in 1959 by Batchelor and co-workers of the penicillin parent compound, 6-aminopenicillanic acid, synthetic derivatives of penicillin have been prepared. Of these compounds, 2,6-dimethoxyphenyl penicillin (Staphcillin) may prove to be of use in the treatment of staphylococcal infections of the newborn (see below). (See also pages 981, 1161.)

Streptomycin is effective against a variety of gram-negative organisms commonly producing infections in newborn infants. It has seemed nontoxic and is frequently utilized with penicillin to produce wide-spectrum antibacterial activity with a low incidence of untoward effects. Streptomycin is bacteriostatic in low concentrations; it may be bactericidal in high concentration, though this effect depends on the organism involved.

Streptomycin is poorly absorbed from the gastrointestinal tract and consequently is not administered by this route in the treatment of systemic infections. It is rapidly absorbed after intramuscular and subcutaneous injection, peak plasma levels being observed in one-half to three hours. The concentration of streptomycin in plasma is nearly twice that present in whole blood, for little of the drug penetrates the erythrocytes. Plasma levels of 7 to 15 micrograms per milliliter are considered sufficient for most streptomycin-sensitive organisms.

Streptomycin is concentrated in the urine, and fairly large amounts are present in liver, muscle and thyroid, with negligible amounts in brain, lung and spleen. It enters the peritoneal fluid readily, the pleural fluid more slowly, and the cerebrospinal fluid with difficulty unless the meninges are inflamed. The drug readily crosses the placenta, and the concentration in fetal plasma is approximately 50 per cent of that in maternal plasma. About one third of plasma streptomycin is protein-bound and unavailable for glomerular filtration.

Approximately 70 per cent of injected streptomycin can be recovered from the urine unchanged within 24 hours in adults. The drug is not excreted by the tubules, and its rate of renal clearance represents about 70 per cent of the glomerular filtrate. One would anticipate decreased renal excretion in newborn infants, though these determinations have not been performed. Small amounts of the drug are found in bile and in feces. The fate of 10 to 30 per cent of parenterally injected streptomycin is not known.

Streptomycin can produce a variety of untoward effects. Damage to the vestibular division of the eighth nerve is common, and deafness may occur; however, if administration of streptomycin is not continued beyond 7 to 10 days, eighth nerve damage is infrequent. Almost all preparations of dihydrostreptomycin, alone or in combination with

other drugs, are no longer available because of the high incidence of deafness associated with their use. Hypersensitivity reactions to streptomycin are rare in newborn infants. The development of strains of bacteria resistant to or dependent on streptomycin is common. This disadvantage is minimized if the drug is given for periods of three to five days, time sufficient for bacteriologic diagnosis and possibly alteration of the therapeutic regimen.

Infants and young children receiving high doses of streptomycin (66 to 165 mg. per kilogram) have sometimes displayed stupor and flaccidity and sometimes coma and deep respiratory depression requiring resuscitation. The same syndrome was observed in rats with acute doses as small as 60 mg. per kilogram[30] (route of administration not stated). In other experiments all adult rats receiving 100 mg. per kilogram died. Those receiving 50 mg. per kilogram, although symptomatic, survived.[30] Reported studies[22] revealed death of adult rats with subcutaneous doses of 750 mg. per kilogram, although symptoms were observed at lower nonlethal doses. Streptomycin by the same route on a weight basis was tolerated slightly less well by the newborn rat than the adult.

Brazil and Corrado[5] have shown that streptomycin is capable of blocking neuromuscular conduction in experimental animals. Loder and Walker[20] reported three cases of a myasthenic state in patients receiving standard doses of streptomycin with relief of symptoms after withdrawing the drug and administering neostigmine. Bush[9] reported a case of persistent neuromuscular block in a six-month-old infant after intraperitoneal instillation of streptomycin sulfate which potentiated the action of a standard dose of D-tubocurarine.

In the newborn and premature nurseries of the Cincinnati General Hospital streptomycin is administered in a dose of 20 to 40 mg. per kilogram per day intramuscularly in divided doses 12 hours apart, though the lower dose has been used more frequently since the recent recommendation of the manufacturer.[29] The drug may also be administered intrathecally in cases of gram-negative meningitis (1 mg. per kilogram). Weinstein[42] recommends a single intrathecal injection of streptomycin in all cases of *Hemophilus influenzae* meningitis. (See also page 1013.)

Broad-Spectrum Drugs

These are so named because of their spectrum and because of their popularity.

Chloramphenicol. Extensive use of chloramphenicol in newborn infants coincided with general availability of means of identifying and following the spread of drug-resistant staphylococci. Observations documenting the acute lethal chloramphenicol collapse in newborn

infants accumulated in many United States and European centers with the administration of chloramphenicol to many infants.[6–8, 18, 19, 35, 36, 43] The United States neonatal death rate rose significantly for the first time in many years.[17] This rise occurred along with the increased use of chloramphenicol in newborn infants, and may have resulted, in part at least, from the use of chloramphenicol. The toxic effect apparently resulted from a number of factors. Extremely high blood levels were attained in infants on the recommended dose. The proportion of circulating drug conjugated as a glucuronide was less than that reported in normal adults. This may have resulted from the decreased conjugating activity of the liver of the newborn infant. Furthermore, chloramphenicol seems to be cleared from the body by tubular excretion of the glucuronide. Of the various renal functions of the infant, tubular activity is one of the least well developed in comparison with more mature subjects; therefore the infant presents a smaller proportion of readily excretable drug to a tubule with decreased activity.[39] A cumulative body retention of the drug results. The microbiologically active unconjugated drug is probably filtered by the glomerulus, but only a small fraction is free and unbound to protein and available for excretion.[39] Current evidence suggests that this lethal effect of chloramphenicol is related to the blood concentration of both conjugated and unconjugated drug. Toxicity studies of conjugated and unconjugated drug have not been reported in detail.[43] Some workers have suggested by analogy with other drugs that toxicity is related to the level of the unconjugated and "undetoxified" drug.[32, 43]

The wide experience with chloramphenicol-associated deaths has resulted in a relatively large body of information on the clinical use of this drug in newborn infants. Weiss and coauthors[43] reported safe doses of 25 mg. per kilogram per day during the first week of life for full-term infants and then 50 mg. per kilogram per day until one month of age. For premature infants they reported safe doses of 25 mg. per kilogram per day for the first month of life. They recommended parenteral intramuscular administration of chloramphenicol sodium succinate, thereby somewhat confusing conclusions drawn from studies on the previously available microcrystalline preparation. They stated that blood levels should be used as a guide to safe and effective therapy if the drug was continued more than four days. This has not proved practical in many centers.

At the Cincinnati General Hospital nonfatal toxic symptoms have been observed on doses of 25 mg. per kilogram per day in infants less than one week of age and weighing more than 2500 gm. The most useful clinical sign has been a sudden fall in body temperature after several days of chloramphenicol therapy. When this sign was noted and the drug was discontinued, the temperature rose within 24 to 36

hours to its previous level, and other signs and symptoms of toxicity disappeared.

Hodgman and Burns[16] reported studies in premature infants and demonstrated the great dose-blood level response variation. Toxic symptoms and elevated blood levels were observed on 25 mg. per kilogram per day in premature infants under one week of age. Inadequate blood levels were observed on 25 mg. per kilogram daily in premature infants treated after one week of age. These authors suggested single daily doses of chloramphenicol sodium succinate to premature infants less than one week of age and 50 mg. per kilogram per day to premature infants over one week of age. The authors also recommended careful observation of the chloramphenicol-treated infant for signs of toxicity. Ziegra and Storm[47] administered 25 mg. per kilogram per day of chloramphenicol sodium succinate intramuscularly in divided doses every 8 hours to premature infants. They reported no toxic symptoms, but concluded that this dose was inadequate for maintaining therapeutic blood levels. They suggested intramuscular administration of 25 mg. per kilogram of chloramphenicol sodium succinate and 25 mg. per kilogram of microcrystalline chloramphenicol at different sites every 48 hours. They thought that premature infants over 4 days of age might require similar dosage every 24 to 36 hours to maintain therapeutic blood levels, but they did not have data to confirm this suggestion. Dorn and Smith[12] reported irregularity of absorption when the palmitate was administered orally.

The clinician is presented with these somewhat conflicting data. In addition, most recent dose-blood level response studies have been reported as nitro compounds. The nitro compounds include (1) the microbiologically active (and unconjugated) fraction of the drug, (2) the glucuronide (conjugated) fraction of the drug, and (3) in studies of the succinic acid ester, the unsplit and inactive succinate ester.

In view of the foregoing, it seems unlikely that both safety and efficacy of chloramphenicol can be predicted on a dose-weight basis in the newborn human infant. It is also unlikely that facilities for microbiological blood assay to assure antibacterial efficacy and chemical blood assay to assure safety will be available to enough physicians to encourage frequent use of chloramphenicol in infants. Perhaps this statement will be made of more antimicrobial agents. (See also page 1027.)

Tetracycline, oxytetracycline, chlortetracycline and demethylchlortetracycline are bacteriostatic drugs which share the same basic chemical structure and have similar antibacterial spectra which include both gram-positive and gram-negative bacteria. Cross resistance is common among drugs of this group. They are excreted in urine and concentrated in bile, although the disposition products do not account for all

the administered drug. When optimum amounts of drug and optimum concentrations of drug are administered orally, absorption is rapid and nearly complete. Baum and associates[3] found that newborn and premature infants required 100 mg. per kilogram daily administered orally at 6-hourly intervals to achieve therapeutic blood levels. Furthermore, there was evidence of drug accumulation and rising serum levels after a week of therapy. Eichenwald and Shinefield[13] stressed caution in continuing oral tetracycline therapy beyond 7 to 10 days. The same workers reported erratic blood levels with intramuscularly injected tetracycline. O'Regan and Schwarzer[27] reported therapeutic levels persisting for 12 hours after chlortetracycline administered in single doses of 3 to 6 mg. per kilogram, though only one patient reported was less than a week of age. (See also page 1001.)

Drugs for the Staphylococcus

These include some old drugs, some new drugs, and some almost discarded drugs.

Erythromycin has a spectrum similar to that of penicillin. Although resistance may develop relatively rapidly, erythromycin has often been used when organisms have been insensitive to penicillin or when penicillin is otherwise contraindicated. Eichenwald and Shinefield[13] cite adequate blood levels achieved with oral administration of 25 to 40 mg. per kilogram per day in newborn infants of the ethyl succinate or the propionyl ester lauryl sulfate. Intramuscular injection of the ethyl succinate produced "adequate blood levels" with 10 mg. per kilogram per day administered in divided doses every 12 hours. (See also page 1115.)

Novobiocin (Albamycin, Cathomycin) is a drug effective against Brucella, Pasteurella, Klebsiella and Proteus, but particularly against *Staphylococcus aureus*. It has been used in treating patients infected with penicillin-resistant staphylococci; but its usefulness has been limited by the ability of these organisms to develop drug resistance. Only a small fraction of novobiocin can be recovered from urine. Furthermore, blood concentration is not greatly elevated or prolonged in patients with renal disease. Bile-serum concentration ratios exceed one, and moderate amounts of the drug can be recovered from feces. Drug recovered from urine and feces, in general, accounts for less than half of the administered dose.

Review of reports of different authors and sequential issues of the *Physicians' Desk Reference* reveal dose recommendations for infants which vary from 12.5 to 160 mg. per kilogram per 24 hours. During a reported staphylococcal outbreak in a nursery, novobiocin was administered in moderate doses (150 mg. daily by mouth) to all infants,

starting immediately after birth.[37] A significant rise in neonatal jaundice was observed with administration of this drug. Studies indicated that novobiocin decreased the ability of the liver to excrete bilirubin, although jaundice resulting from red cell destruction was not excluded.

Teixeira and Scott[41] demonstrated therapeutic blood levels of novobiocin in newborn infants after oral administration of a single dose of 12.5 mg. per kilogram in a study of 9 patients. Birth weights were between 4 pounds 5½ ounces and 5 pounds 15 ounces. In infants 4 days old or less the peak blood levels varied between 18 and 90 micrograms per milliliter, and the younger the infant, the higher the level. There was a less clear inverse relation between birth weight and serum level.

Clinical indication for the use of novobiocin is mild disease caused by a penicillin- and erythromycin-resistant strain of *Staphylococcus aureus.*

Bacitracin is a bactericidal and bacteriostatic drug to which gram-positive bacilli, clostridia, some strains of *Hemophilus influenzae,* and gram-positive cocci are susceptible. Perry and co-workers[28] used this drug in infants and young children suffering from life-threatening infection with penicillin-resistant staphylococci. The main known route of disposition of bacitracin is the kidney, and renal excretion has corresponded to the rate of glomerular filtration in at least some of the studies in animals and human adults. Early clinical experience demonstrated that a large proportion of older patients treated with systemic bacitracin suffered albuminuria or other renal abnormality. This response was related to daily dose as well as to patient susceptibility. Eichenwald and Shinefield[13] reported use of bacitracin in nearly 100 infants for periods up to 10 to 12 days without a single instance of renal findings severe enough to necessitate discontinuing the drug. Experience with the use of bacitracin in infants and small children at the Cincinnati General Hospital and the Children's Hospital in Cincinnati has not indicated a significant incidence of bacitracin-induced renal complication. The explanation for the apparent difference in toxic response in infants and in adults could be decreased nephrotoxicity of currently produced bacitracin preparations, or perhaps an instance of decreased drug toxicity in the less mature human being.

Eichenwald and co-workers[13] found that peak blood levels were reached 2 to 4 hours after intramuscular injection, and antibacterial activity persisted in the serum for 10 to 12 hours. They suggested 1000 units per kilogram per day administered at 8- or 12-hour intervals for the infant over 2500 gm. and 900 units per kilogram per day administered at 8- or 12-hour intervals for the infant under 2500 gm. Diluted bacitracin increases in toxicity at refrigerator temperature and so should be stored at 4° C. and discarded after 2 days. (See also page 1067.)

Dimethoxyphenyl penicillin (DIMOP penicillin) gives promise for the patient infected with penicillin-resistant strains of *Staphylococcus aureus,* although there is limited reported pediatric experience with this relatively new drug. The drug is not inactivated by staphylococcal penicillinase, the enzyme which renders some naturally occurring coagulase-positive staphylococci resistant to penicillin. Furthermore, evidence indicates that fewer coagulase-positive staphylococci are resistant to DIMOP penicillin than were resistant to penicillin G in some of the first laboratory and clinical reports: only one in about 5000 of naturally occurring coagulase-positive staphylococci studied have proved resistant to DIMOP penicillin. The resistance of these strains has resulted from mechanisms other than increased penicillinase production. Resistant strains have been developed in vitro only with difficulty and are of questionable clinical significance.

DIMOP penicillin is inactivated by acid and therefore must be administered intravenously or intramuscularly. The principal known site of disposition is the kidney, though not all the administered drug can be recovered from the urine. Larger amounts of the drug must be administered, for it is less potent than other penicillin compounds on a weight basis, although its resistance to staphylococcal penicillinase renders it more active against penicillinase-producing staphylococci. The drug is rapidly absorbed from intramuscular sites in adult patients and older children and is rapidly cleared from the blood, thereby necessitating intramuscular administration every three or four hours. Stewart and co-workers[34] treated 17 children with DIMOP penicillin (only 2 of the 17 reported children were under 2 weeks of age). They used 100 mg. per kilogram each day given in 4 equal 6-hourly doses. Day and co-workers[11] administered single doses of 125 and 250 mg. to newborn infants at birth and prevented staphylococcal colonization in most of the infants until the third day, but not until the fourth day of life, suggesting that the drug was cleared less well by the infant than by the older patient. Furthermore, on the third or fourth day the drug could be recovered from the urine of 20 per cent of the infants receiving 250 mg. In children peak levels were attained at 30 minutes when using 25 or 50 mg. per kilogram, the range falling within the "therapeutic level." (An amount of 3 to 6 micrograms per milliliter is usually inhibitory in vitro.) By 3 hours the blood level had fallen so that the lower limit of the range fell below the "therapeutic level" even when 50 mg. per kilogram had been administered. Among the patients treated by Day and co-workers with these drug doses were three children less than one week of age. One with a meningomyelocele died.

Although these two studies do not prove the proper dose for the newborn infant, there is a suggestion that the newborn may require smaller

doses than the older patient. Perhaps unjustified reassurance for the larger doses is obtained by the fact that in preliminary studies a larger amount of DIMOP penicillin than penicillin G is required to kill 50 per cent of newborn rats.[40]

Drugs for Gram-Negative Organisms

These are of vital importance to the physician treating bacterial infection acquired before birth.

Polymyxin B is the agent of this family of antimicrobial agents which is available in the United States. It is active against gram negative bacteria and on a weight basis is the most potent antimicrobial agent against *Pseudomonas aeruginosa*. It is bactericidal even in the absence of dividing cells, altering function of the bacterial cell wall so that osmotic dysequilibrium results. Bacterial resistance to this drug develops slowly.

Renal toxicity and neurotoxicity are the most troublesome of the symptoms accompanying polymyxin therapy, although neurotoxic symptoms are not frequently observed in the infant. Apparently renal changes are reversible if the drug is promptly discontinued after detection of albuminuria, increased formed elements in the urinary sediment, or rising blood urea nitrogen.

Polymyxin B diffuses poorly into body cavities and must be administered locally for optimum antibacterial effect. Systemic administration, which should be only by the intramuscular route, is indicated when Pseudomonas sepsis has been proved or is suspected to accompany proved local Pseudomonas infection. The principal known site of drug disposition is the urine—up to 60 per cent of administered dose has been recovered. Polymyxin B must be administered intrathecally in meningitis due to Pseudomonas, for it does not cross the cerebrospinal fluid barrier.

Polymyxin B in dosages of 2.5 mg. per kilogram per day in full-term infants more than 2 weeks of age may result in slight transient albuminuria.[13] Doses of 1.0 to 1.5 mg. per kilogram daily for periods not exceeding one week in term-sized and in premature infants are "reasonably safe and effective." Even in infants drug fever or rash may be noted. In meningitis, 1.5 mg. in 3 ml. of 0.9 per cent saline are administered daily by the intrathecal route. (See also page 1057.)

Neomycin administered parenterally is frequently associated with deafness and renal abnormalities. The renal abnormality is notably found in patients with pre-existing decreased renal function. Thirty to 50 per cent of parenterally administered drug can be recovered from the urine, whereas 3 per cent or less of orally administered drug can be found in the urine. Poor absorption of the drug from the gastrointestinal tract has resulted in its use in the treatment of infantile

diarrhea associated with enteropathic strains of *Escherichia coli*. Oral doses of 50 to 100 gm. per kilogram daily are used. There may be partial absorption of the drug from the gastrointestinal tract, so that prolonged administration should be avoided.

Occasionally, at least in older patients, the drug has been administered parenterally when systemic or urinary tract infection has shown a sensitive Aerobacter, Proteus or similar organism, and drug sensitivity testing of the organism has revealed no therapeutic choice other than neomycin. (See also page 1049.)

Kanamycin is active against a variety of gram-positive and gram-negative bacteria. Yow and Womack[46] used the drug to treat patients infected with penicillin-resistant staphylococcus. Because the drug is active against most gram-negative organisms, including some strains of Proteus and Pseudomonas, Eichenwald has chosen this drug as one of his agents of choice in the treatment of neonatal infections.

Kanamycin is bactericidal in the presence of proliferating cells. Bacterial resistance develops more slowly than with streptomycin, a drug with a similar antibacterial spectrum, but without cross resistance. Toxicity is less than with neomycin, another drug with a similar antibacterial spectrum, but with cross resistance.

The principal known site of drug disposition is the urine, 27 to 88 per cent of intravenously administered doses having been recovered from the urine of dogs. There is some drug concentration in bile.

Toxic effects on the inner ear and on the kidney are recognized, renal abnormalities having been reported in 100 per cent of 20 men who received 50 mg. per kilogram, and hearing loss in 50 per cent of the same men.[44] Casts, albuminuria, or hearing loss were reported in 12 of 41 children of High and coauthors.[15] Yow and Womack[46] noted rising blood urea nitrogen terminally in treated children who died. They also reported intermittent cylindruria when more than 50 mg. per kilogram per day was administered.

Among the children of Yow and Womack[46] there were 10 infants of one week of age or less who received 10 to 100 mg. per kilogram daily. Four of these 10 infants died, though all but one of the 4 were either moribund at the onset of treatment or had morphologic explanations for death at autopsy.

High and co-workers[15] reported dose-blood level response in older children and suggested doses of 10 mg. per kilogram repeated every 6 to 8 hours, or 20 mg. per kilogram repeated every 8 to 12 hours.

Baum and associates[4] found that 7.5 mg. per kilogram produced serum concentrations of 15 to 20 micrograms per milliliter with clearance to 1 to 3 micrograms per milliliter by 12 hours in premature infants. They therefore suggested 7.5 mg. per kilogram every 12 hours. They found this dosage schedule suitable for full-term infants as well. A small proportion of infants had albuminuria which disappeared

when the drug was discontinued, although kanamycin was never continued longer than 12 days. Follow-up of 40 kanamycin-treated infants did not reveal evidence of either hearing loss or renal damage. (See also page 1043.)

Colistimethate was discovered in Japan and has been used in other countries for several years. It resembles the polymyxins in that it is a polypeptide; however, the amino acid composition is enough different that it is not called a polymyxin. It is active against a number of gram-negative organisms, including most strains of *E. coli* and many strains of Paracolobactrum and Pseudomonas, and some strains of A. *aerogenes*. Proteus strains are relatively insensitive. Bacterial resistance does not develop readily, and the drug is said to be well tolerated. It is rapidly absorbed after intramuscular injection, and some is excreted in the urine.

Experience with colistimethate in children is limited. Ross and coauthors[31] presented blood levels in 4 children (no infants) and suggested that 7.5 mg. per kilogram per day be administered intramuscularly at 6-hour intervals. These workers treated 11 infants who were 7 months of age or younger. Eight of these infants received only 2.5 mg. per kilogram daily intramuscularly, and 5 of these 8 showed somewhat elevated blood urea nitrogen levels. Three of the 11 infants treated received 15 mg. per kilogram per day orally. The blood urea nitrogen was elevated in two of the three infants.

Although this drug may prove useful in the therapy of neonatal infections caused by gram-negative organisms, present data do not justify its widespread clinical use. It is of interest that colistimethate is better tolerated by the newborn rat than by the adult rat. This is not true of mice.[38] (See also page 1065.)

SUMMARY

The newborn infant more often acquires life-threatening bacterial infection than more mature human patients. The signs of this infection may be subtle and manifested only when death is imminent. Therefore the physician cannot always delay antimicrobial therapy until signs of infection are obvious. The thoughtful physician, however, withholds antimicrobial therapy until specimens adequate for making a specific bacteriologic diagnosis have been obtained. Whether or not antimicrobial agents in therapeutic doses are begun depends on consideration of the factors predisposing the infant to serious infections. The choice of drugs will depend upon the source of the infection and the likely offending organisms. When bacteriologic and drug sensitivity data in vitro are known, the ideal drug or drugs should be given.

The physician cannot have a complete knowledge of every drug or

combination of drugs. The limited resources will therefore consist of scrutinized drugs. Scrutiny should continue, and every failure must be reviewed to determine whether death or disease resulted because of drug use or in spite of it.

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ANTIMICROBIAL THERAPY IN STAPHYLOCOCCAL DISEASE OF CHILDREN

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Effective antimicrobial therapy of staphylococcal infection in children must be based on a knowledge of the antibiotic resistance of the infecting organism. Resistance patterns will vary from time to time and from place to place and will depend on the source of the infection.

This problem of antibiotic resistance in staphylococcal infection in childhood does not differ in essentials from that in patients of any other age, but it may be posed more sharply in the newborn by the insidious onset of clinical signs and by the urgency of therapy.

Empirical administration of antibiotics is to be deplored. The aim of the paediatrician should be to seek the co-operation of the laboratory so that the infecting organism can be isolated and its antibiotic sensitivities determined. There are, however, many occasions when therapy cannot wait upon the results of these tests, and in these cases the therapy with the best chance of success must be used until the results are available and may then be changed if necessary. In order to decide the therapy with the best chance of success, a knowledge of where the child acquired its infection and of the staphylococcal strains commonly circulating there is invaluable. Strains acquired in a hospital are more likely to be resistant to a wider range of antibiotics than are those acquired in the home or at school; even so, this generalization has its limitations.

It is for these reasons that we propose to consider in this article the ecology of the staphylococcus in the maternity nursery, the paediatric hospital and the home and to discuss the problem of antibiotic

resistance in these bacteria before we consider the therapy of particular types of clinical infection. Throughout, when we speak of staphylococci, we refer to coagulase-positive *Staphylococcus aureus*.

COLONIZATION AND INFECTION IN THE HOSPITAL NURSERY

The baby born in a hospital encounters very rapidly the staphylococci of its environment and within a few days of birth may become colonized with these organisms. The first sites of colonization are the umbilicus, the moist umbilical cord and the groins, and by the time the cord has separated, the cocci are established in enormous numbers in the anterior nares.[6, 9] The actual number of babies colonized varies from hospital to hospital and depends on the methods of handling the babies. In some hospitals 90 per cent of babies have been found to be nasal carriers at the end of the first week of life. In others, where measures designed to prevent or postpone the carrier state have been adopted,[8] 30 to 38 per cent have become carriers within 10 days of birth.

The staphylococci acquired by the hospital baby are rarely those of its mother. The strains found usually correspond to those of the nursery staff and to those in other babies in the same nursery. Investigations using phage typing have shown that in non-epidemic periods many different phage types may be present in the babies' noses; in epidemic periods a high proportion of babies may be colonized by the particular epidemic strain, which may also be isolated from many parts of the nursery, from the bedding and from the nursery staff.

Not all colonized babies acquire clinical infection. Whether they do or not depends to some extent on the strain acquired. For instance, Fekety et al.[5] found that 70 per cent of 49 babies colonized with an epidemic strain of phage type 80/81 had clinical infection either while they were in the nursery or after they had gone home, while only three of 92 babies from the same nursery colonized with a variety of other strains had clinical infections.

SPREAD OF STAPHYLOCOCCI IN THE HOME

Babies colonized in the maternity hospital may not have a clinical illness until after they have gone to their homes. There is no doubt, however, that in many babies the origin of their infection lies in the hospital. In a series of 20 children who died of staphylococcal pneumonia in a children's hospital in Melbourne in 1953,[18] sixteen were aged less than 6 months, and 10 were admitted to hospital either directly from or within a few days after discharge from maternity units.

Colonized babies may also be responsible for the spread of infection

to other members of their families, particularly if they have acquired an "epidemic" strain in hospital. Hurst and Grossman[10] studied a large sample of the families of infants born in a hospital during an outbreak of type 80/81 infection. They estimated that clinical infection had spread to approximately half of these families, mothers, fathers and siblings being affected. It is difficult to obtain exact figures for the extent of such family spread, which will depend on such factors as the infectivity of the introduced strain, the standard of hygiene in the home and the numbers of siblings at risk. Minor infections and carrier states may persist in a family for long periods of time before the occurrence of more severe illness such as staphylococcal pneumonia in a sibling of the infant who originally introduced the infection. Nevertheless, clinicians can recognise what may be aptly called "staphylococcal families" in which there is a long history of recurrent lesions, such as boils, carbuncles and infected lacerations and insect bites, in one member of the family after another. These families frequently date the onset of their staphylococcal plague from the birth of a baby.

There are, of course, other ways by which the staphylococci may be introduced into the home. An older child may bring the infection home from school. Adults particularly exposed by their occupation to the hazard of infection may be the source of a family outbreak. A dermatologist of our acquaintance was infected in his practice and thereafter was able to trace a chain of infection to his own children and thence to the children of four other families in the neighbourhood.

INFECTION IN CHILDREN'S HOSPITALS

Apart from patients admitted to the paediatric hospital suffering from staphylococcal disease, there is also the possibility that children admitted for the treatment of other illnesses may become cross-infected with "hospital" staphylococci. Such cross-infections include those of surgical wounds, of the skin and subcutaneous tissues, or may take the form of pneumonia or entero-colitis. These infections do not differ in their aetiology and methods of transmission from those of adults similarly cross-infected in hospital.

ANTIBIOTIC-RESISTANT STAPHYLOCOCCI

It was not long after the introduction of penicillin that Colbeck[3] reported a widespread epidemic of pustules in babies and breast abscesses in their mothers due to a particular penicillin-resistant strain of *Staph. aureus* that occurred in Winnipeg hospitals in 1947–49. Since then numerous nursery outbreaks caused by penicillin-resistant strains have been reported. Particularly notorious as a cause of nursery epidemics

are strains of phage type 80 or 80/81, first recognized in Australia in 1953,[15] and first observed in the United States in 1954,[17] in Great Britain in 1955,[4] and in New Zealand in 1955.[1]

Penicillin-resistant staphylococci isolated from patients suffering from clinical infection or from carriers are resistant because they produce the penicillin-destroying enzyme penicillinase. Early in the appearance of penicillin-resistant staphylococci as a problem in hospitals, it was recognised that in individual hospitals only a few resistant strains were circulating and were responsible for most of the hospital infections. Since then, the introduction of any new antibiotic has been followed by the appearance of mutants resistant to it. Although the biochemical changes that allow the mutants to by-pass the metabolic pathways affected by the antibiotics are not clearly understood, the genetic basis of these mutations is well established and the mutation rates have been measured for some antibiotics.

Since each mutation is the result of a single genetic event, the chance occurrence of a mutant simultaneously resistant to two antibiotics is very small, being the product of the chances for the two individual mutations. It is for this reason that simultaneous therapy with two antibiotics is now widely used in an attempt to prevent the further development of resistant strains.

The first strains isolated in hospitals that showed multiple resistance to antibiotics belonged to phage group III, but in recent years strains belonging to other phage groups have displayed multiple resistance. Of pertinence to the present discussion is the fact that in the United States and Great Britain the phage type 80/81 strains, that are a frequent cause of nursery epidemics, are resistant to penicillin and tetracycline, frequently to chloramphenicol and erythromycin[2] and sometimes to novobiocin.[16] The degree to which the type 80/81 strains in any one hospital have become resistant to chloramphenicol, erythromycin and novobiccin is correlated with the extent to which these antibiotics have been used in therapy.

Because of their epidemic nature these type 80/81 strains have been widely publicized and studied, but it should be stressed that many other phage types of *Staph. aureus* can produce sporadic clinical infection of infants and older children and, on occasion, cause nursery epidemics. Further, there is no certain correlation between phage type and antibiotic sensitivity pattern. Since phage typing of *individual* strains is of no therapeutic value, this specialized technique should be reserved for the investigation of hospital epidemics or for particular research projects.

Table 30 summarizes some recent figures for resistance to antibiotics among strains obtained from clinical infections in children of various age groups in hospital and not in hospital. These figures were obtained

TABLE 30. *Percentage of Staphylococci Resistant or Sensitive to Antibiotics, Isolated from Children of Various Ages Inside and Outside Hospitals*

COUNTRY	TYPE OF PATIENT	DATE	NO. OF CULTURES	% PENICILLIN-SENSITIVE	% RESISTANT TO P*	S*	T*	C*	E*	REFERENCE
Australia	Neonates in hospital	1960–61	39	28	72	2	5	7	5	Personal observations
	Children outside hospital:									
	0–1 year	1958	47	17	83	2	2	—	—	Johnson et al.[11]
	1–4 years	1958	127	41	59	1	—	—	—	
	Children in hospital	1959–60	527	21	79	17	24	—	—	Dorman
	Children outside hospital	1959–60	109	46	54	2	4	—	—	
Finland	Children in hospital	1958–59								
	<1 year		36	8	92	63	53	3	—	Mäkelä[14]
	1–15 years		38	25	74	22	5	3	—	
Germany	Hospital infection	1955–56	56	7	93	68	10	—	—	Linzenmeier and
	Home infection	1955–56	60	23	77	40	2	—	—	Zeit[13]

* *P*, penicillin; *S*, streptomycin; *T*, tetracycline; *C*, chloramphenicol; *E*, erythromycin.

during studies in Finland, Australia and Germany. They serve to illustrate the point that the incidence of resistant strains varies from place to place and in various age groups and can be taken as a guide to therapy only in the particular place where the observations were made.

The extent to which hospital strains have spread in a community will determine the antibiotic resistance of the infecting strain in an individual child with no history of recent contact with a hospital. For example, a survey of infections of the skin and subcutaneous tissues seen by general practitioners in Australia in 1958 showed that while 83 per cent of the staphylococci isolated from infants under one year of age were penicillin-resistant, this percentage fell to 59 per cent in children aged 1 to 4 years and to 50 per cent in those in the 5 to 9 age group.[11] These results were interpreted as indicating that the source of the infants' strains was the maternity hospital, while those in older children were more likely to be a sample of those circulating in the schools, as well as those derived from younger siblings.

INFECTIONS IN THE NEWBORN

Clinical Conditions

Staphylococcal infections in babies in the first months of life are almost invariably acquired in the hospital nursery in countries where babies are born in hospital. Most infections are mild, and the skin and its adnexa, and the conjunctiva are the commonest sites involved. The time of maximum incidence is at the end of the first week and during the second week of life, although skin lesions and pneumonia may, on rare occasions, be observed at birth.

Pustules, or *pyoderma*, are small vesicular lesions, yellow because of contained pus, which appear predominantly in the folds of the skin. They are often dismised as a "heat rash" or "napkin rash," but must also be differentiated from milia, which occurs mainly on the nose and chin in the first few days of life and in which the individual lesions are never larger than a pin's head. In epidemics, and occasionally sporadically, there is a tendency for the pustules to have more cellulitic reaction than usual and to form abscesses.

The aetiology of the pustule is almost always staphylococcal, and a positive culture is readily obtained from the pus. Abscesses of the breast, neck and other sites are usually staphylococcal and of serious import.

Infection of the umbilicus is often diagnosed when the stump is moist and staphylococci are isolated on culture. One may, however, doubt whether this diagnosis is always correct, since the umbilicus is so often colonized in the newborn. Antibiotic therapy is required only when there is reddening or evidence of pus.

Doubts on the staphylococcal aetiology of the "*sticky eye*" may well be entertained. The conjunctiva is frequently infected, usually mildly, but not always with staphylococci. When frank pus is present, the staphylococcus is commonly the responsible agent.

Paronychia is invariably staphylococcal. In its mild form, only slight redness around the base of the nail is evident. Frank pus formation with widespread erythema is to be regarded as a serious sign.

Infection may occur at the site of skin damage; cutdown sites and other surgical wounds and the umbilicus after exchange transfusion by this route are examples. These infections are usually mild, but may extend locally; rarely, umbilical infection may extend to the liver.

Sporadic *impetigo* of the newborn is not common, but epidemics occur. The individual lesions are superficial and may be vesicular or bullous. The overlying skin is easily damaged, leaving a moist reddened area. Pemphigus neonatorum is diagnosed when these lesions are widely distributed on the baby's body. The baby is very ill and has a poor prognosis. Differentiation from the rare epidermolysis bullosa is possible only in retrospect; in the latter condition staphylococci often become secondary invaders and require antimicrobial therapy.

Staphylococcal pneumonia, osteomyelitis and septic arthritis are the commonest of the serious infections in the neonatal period.

Pneumonia following viral infection of the respiratory tract is almost invariably staphylococcal. The usual sequence of events is as follows:

1. Profuse nasal discharge occurs, at first mucoid, later purulent, and usually unaccompanied by any constitutional disturbance.

2. Extension beyond the nose is manifested by a dry cough. At this stage the baby may begin to show mild deterioration in its general condition, with anorexia and fever.

3. Evidence of pulmonary involvement occurs with cyanosis and tachypnoea, commonly accompanied by an expiratory grunt. The baby is sick and distressed and usually has a high fever. Harley[7] drew attention to the association of abdominal distension with staphylococcal pneumonia, with or without anorexia, vomiting or constipation; on occasions a mistaken provisional diagnosis of intestinal obstruction has been made.

The first two stages may take as long as 7 to 10 days to merge into the third. At other times they may be unrecognisable, and death may occur within 24 hours of the first symptoms.

Physical signs of pneumonia or empyema may be elicited, but are notoriously unreliable in the small baby. Indeed, radiological evidence of pulmonary and pleural involvement is often found without any definite clinical signs. Empyema and pulmonary abscesses complicate the pneumonia in the majority of cases, and emphysematous bullae of the lung or tension pneumothorax may develop dramatically and lead to sudden death from respiratory and cardiac insufficiency.

Osteomyelitis or *septic arthritis* may occur with obvious constitutional disturbance, but apparent inability to move a limb without any other signs is not uncommon, leading to a mistaken diagnosis unless the clinician is well aware of this possibility. A careful examination for an area of bony tenderness or swelling should be made, followed by radiological examination. A lead to the diagnosis may be given by the presence of minor skin infection, but the absence of this does not exclude osteomyelitis.

Antibiotic Therapy

Is an Antibiotic Indicated? There are many reasons for avoiding the use of antibiotics when this may be done without jeopardising the welfare of the patient, and nowhere are these reasons more cogent than in the neonate. Toxic effects of many drugs, including antibiotics, have been described in recent years, the latest being the serious effect of chloramphenicol on young infants, particularly premature ones. Problems of bacterial resistance have increased, and it is accepted that this is closely related to the exhibition of antibiotics.

Nevertheless, to advise that only obviously serious infections should be treated with antibiotics is not acceptable. Apparently mild infections may progress so rapidly that they claim, or at least threaten, the life of the baby. This is more likely to occur during a nursery epidemic than sporadically, and therefore it is advisable during an epidemic to give antibiotics to all babies with suspected staphylococcal infection.

In the absence of an epidemic, mild infection (single superficial pustules, sticky eyes, the moist umbilicus, slight redness around the nail bed) may be safely treated with local measures. Should there be any evidence of more severe infection (cellulitis around pustules, a suggestion of abscess formation or paronychia with notable redness) or any deterioration of the infant's condition, systemic antibiotic therapy is indicated. When there is no doubt that the baby has a serious infection, antibiotic therapy is obligatory.

The Choice of Antibiotics. Before therapy is commenced every attempt should be made to isolate the infecting organism. Antibiotic treatment must often start, however, before the results of sensitivity tests are available, and, indeed, the infecting organism may never be isolated.

In discussing empirical antibiotic therapy, generalizations may be fallacious. An antibiotic or combination of antibiotics appropriate in one hospital may be quite useless in another. For example, type 80/81 strains isolated by Schreck and Hopps[16] in Philadelphia from patients, including infants, were 99 per cent resistant to penicillin, 100 per cent to streptomycin, 95 per cent to tetracycline, 75 per cent to erythromy-

cin, 47 per cent to novobiocin, 29 per cent to chloramphenicol and 8 per cent to neomycin. Empirical treatment of a suspected staphylococcal infection in their hospital might well differ from that in other places.

During a nursery epidemic, knowledge of the antibiotic sensitivities of strains isolated from *early* cases will be of great value in choosing the appropriate antibiotics.

Table 31 summarizes the main advantages and disadvantages of the commonly used antibiotics and the indications for their use.

Penicillin is rarely useful, and even when the staphylococcus is found to be sensitive to it on first testing it is occasionally found that, following penicillin therapy, the same organism is resistant 24 hours later.

A combination of antibiotics is recommended for serious infections, erythromycin and novobiocin being preferred. With this combination low toxicity is an advantage. It is realised that other combinations are widely used and considered satisfactory, e.g., streptomycin with chloramphenicol, erythromycin or tetracycline, or chloramphenicol with erythromycin, but novobiocin and erythromycin combine effectiveness with minimum toxicity.

Methicillin is worthy of special discussion, since it is an important advance in the therapy of resistant staphylococcal infections, owing to the fact that it is not affected by staphylococcal penicillinase. It is bactericidal and non-toxic. In hospitals its use might reasonably be restricted to the treatment of infections proved to be resistant to penicillin, streptomycin, tetracycline, erythromycin, and novobiocin. The exception to this restriction would be life-threatening infections in which the staphylococcus can confidently be held as the responsible agents, e.g. pneumonia with empyema or osteomyelitis. Indiscriminate use of methicillin can only be condemned, and its use in sprays to control staphylococci in wards can hardly be defended; resistant strains have already been isolated from adult patients.

INFECTIONS IN PAEDIATRIC HOSPITALS

Some of the children in paediatric hospitals will have acquired their infection outside hospitals rather than in hospitals or nurseries. The incidence of multiple resistant strains may therefore be less than it is in neonatal infections and the choice of an antibiotic not so difficult.

The staphylococcal infections most commonly seen are skin infections such as furuncles, abscesses, cellulitis and paronychia, acute osteomyelitis and septic arthritis, pneumonia, wound and burn sepsis, septicaemia. Rarely, bacterial endocarditis is staphylococcal, and an occasional case of staphylococcal meningitis may be seen.

TABLE 31. *Advantages and Disadvantages of the Antibiotics Commonly Used for Staphylococcal Infection in Children*

ANTIBIOTIC	ADVANTAGES	DISADVANTAGES	INDICATIONS
Penicillin	Bactericidal; nontoxic; most efficient agent available; narrow spectrum	Organism rarely sensitive	When sensitivity of organism proved
Tetracycline	Safe, relatively nontoxic. Resistance develops slowly	Resistance not rare. Broad spectrum leads to suppression of other flora	May be used alone in less serious infections or when previous knowledge suggests likely sensitivity
Streptomycin	Bactericidal, effective	Resistance develops rapidly. Must be given intramuscularly. Toxic to 8th cranial nerve	Used in combined therapy, only when sensitivity is known
Erythromycin	May be bactericidal in high concentrations. Nontoxic; very effective; narrow spectrum	Resistance develops rapidly	Must never be given alone. Used in combination for serious or potentially serious infections often before sensitivity tests available
Novobiocin	Low toxicity; narrow spectrum; effective	Bacteriostatic. Resistance develops rapidly	
Chloramphenicol	Resistance unusual and develops slowly. Effective. Penetrates to cerebrospinal fluid	Toxic: (1) Bone marrow depression. (2) "Grey syndrome." Broad spectrum; bacteriostatic	Rarely indicated in first month of life, and only when sensitivity proved and other effective agents not appropriate
Vancomycin, ristocetin	Bactericidal; highly effective. Resistance as yet unrecorded	Must be given intravenously. Toxic to 8th cranial nerve, mainly in presence of renal failure	Given alone for serious infection with staphylococci resistant to other antibiotics
Methicillin	Bactericidal; nontoxic; effective; resistance very rare	Must be given intramuscularly every 4–6 hours due to rapid excretion	See text
Kanamycin	Resistance rare	Toxic to 8th cranial nerve. Cross-resistance with neomycin and partial cross-resistance with streptomycin	Toxicity precludes use apart from exceptional circumstances. Not advised in presence of renal insufficiency

Skin Infections

The clinical picture of these is so well known that a precise description is hardly necessary. There is a tendency to spread or recurrence unless careful local measures are used, and the necessity for surgical treatment and drainage must not be overlooked. The use of antibiotics may abort the infection and prevent frank pus formation, but once pus has formed, antibiotics alone will be inadequate.

When the infection is minor, the use of antibiotics may be avoided without serious consequences. Therapy is advisable, however, for minor infections in the first year of life and, at any age, when cellulitis or deep abscess formation is present. Nowadays, penicillin has at best only a 50-50 chance of success and should be used only when bacteriological studies have indicated that the organism is sensitive to it. Tetracycline is the drug of first choice for minor infections, but may be changed later if the infecting organism is resistant to it.

If the infection is serious, erythromycin and novobiccin is the combination recommended.

Acute Osteomyelitis and Septic Arthritis

The staphylococcus is the infecting organism in over 95 per cent of these cases. The onset is usually abrupt with fever and constitutional disturbance. Pain, inflammation and local tenderness may be evident from the outset when the bone involved is superficial. Infections of the hip or femur, which are common, offer a more difficult diagnostic problem, particularly in the infant. Unwillingness to use the limb may suggest a diagnosis of poliomyelitis, and joint involvement with signs of inflammation after the age of two or three years requires differentiation from monarticular rheumatism.

Most children admitted to hospital have already received an antibiotic, commonly penicillin or tetracycline, and the clinical picture may be less dramatic and the diagnosis less obvious. Blood cultures may have been rendered negative and the chance of isolating the infecting organism lost. Nevertheless, blood cultures should always be carried out before therapy is started.

Effective early treatment is of great importance, and a combination of erythromycin and novobiocin is recommended. They should be given parenterally in severely toxic children or when the child is vomiting. When the toxaemia is extreme or when there is no response to erythromycin and novobiocin in 48 to 72 hours, methicillin should be used.

The role of surgery should never be overlooked in this disease.

Pneumonia

This is predominantly a disease of infants. For example, of 32 affected children seen by Harley[7] at the Royal Alexandra Hospital for Children, Sydney, 12 were less than 3 months of age and 28 less than 2 years. The majority were admitted during the winter. Staphylococcal pneumonia is a common illness in infants suffering from fibrocystic disease of the pancreas.

The clinical picture of staphylococcal pneumonia has already been described in the section on neonatal infections, and there are no significant differences in children admitted to paediatric hospitals. The antibiotic treatment is the same as that in osteomyelitis.

When is pneumonia staphylococcal? Empirically, for the purpose of treatment, all infants under one year with pneumonia should be regarded as infected with staphylococci, and nearly all between the ages of one and two. Older children with severe toxicity should be similarly regarded. Attempts to isolate the infecting organism, including blood culture and culture of pus from empyema, should be made before therapy is commenced. Laryngeal swabs are valuable for obtaining material for culture.

Wound and Burn Sepsis

Sepsis of this sort is a problem in paediatric hospitals just as it is in general hospitals. Treatment of frank infections with an appropriate antibiotic is desirable unless the infection is well localised, but the use of systemic antibiotics for prophylaxis serves little purpose and may be a potent source of resistant strains.

Septicaemia

The infant or child who is seriously ill without obvious cause will sometimes be found to be suffering from staphylococcal septicaemia. Superficial skin lesions may or may not be present, and their absence in no way precludes the possibility of septicaemia. The clinical picture is one of extreme toxicity and high fever with rigors. Circulatory collapse often develops, and, indeed, may be the presenting sign.

Blood cultures are essential for diagnosis. Difficulty is sometimes met in differentiating a primary staphylococcal septicaemia from rheumatoid arthritis presenting with severe toxaemia. Joint pain and swelling may develop in both, as may rigors, splenomegaly and pericarditis. When the diagnosis is in doubt, treatment for septicaemia is necessary while awaiting the results of blood culture.

Prompt therapy is called for. The antibiotics of choice are vancomycin or methicillin.

Bacterial Endocarditis

This is fortunately not common, although the incidence has risen slightly since the introduction of cardiac surgery. The diagnosis of endocarditis should be considered when an unexplained fever persists in a patient who has an organic heart murmur, or who has just undergone cardiac surgery; blood cultures must be taken.

Therapy with a bactericidal agent is essential to improve the chance of sterilization of the heart lesion. Vancomycin for a prolonged period of not less than three weeks is advisable. Methicillin may prove of great value in these cases.

INFECTIONS IN THE HOME

The commonest lesions seen in general practice are furuncles, abscesses, paronychia, impetigo, infected lacerations, carbuncles, pustules and cellulitis.

Many staphylococcal infections in the home may safely be, and often are, treated without systemic antibiotics. When an antibiotic is considered necessary, tetracycline is the drug of choice, unless the organisms have been shown to be sensitive to penicillin.

The more serious infections are discussed under previous headings. Perhaps all children with serious infections should be treated in hospital.

COMMENT

Writing on the rationale and management of combined therapy, Lacey[12] remarked that "there is almost no evidence to assess because the present practice of chemotherapy has been developed largely by trial and error and under the influence of local fashion and publications of persons with a financial or emotional interest in a particular drug or mode of therapy." One is inevitably influenced by local fashion, by advertising pressure and, perhaps even worse, by "clinical impression" which in the confusing field of antibiotics must colour one's thoughts and actions very much. The lack of objective evidence in antibiotic therapy is such that only opinions can be stated, and no generalization about the most suitable antibiotic is applicable to all circumstances.

Nevertheless, the following principles on which antimicrobial therapy of staphylococcal disease should be based may be stated:

1. Every attempt should be made to isolate the infecting organism so that antibiotic sensitivity tests can be done.
2. Bactericidal agents are to be preferred to bacteriostatic ones.

3. In severely ill children, combinations of the antibiotics most likely to be effective should be given.

4. Antibiotics should not be used for the treatment of minor infections in children over the age of one year.

5. The newer antibiotics should be used as seldom as posible so that their therapeutic efficiency may be retained.

6. Combinations of antibiotics should be used to delay the emergence of resistant strains.

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MANAGEMENT OF BACTERIAL MENINGITIS IN CHILDREN

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The management of acute bacterial meningitis has not changed greatly during the last decade.[1, 6, 11, 31, 46, 48] Results depend upon prompt diagnosis, administration of specific antibacterial agents, and the usual supportive measures. Some controversy exists over the advisability of using multiple antibiotics,[6] or a single specific antibiotic[19] selected on the basis of clinical observation and cerebrospinal fluid findings, but most clinicians prefer to begin therapy with a combination of penicillin, sulfonamides and either chloramphenicol[1, 11, 31, 46] or tetracycline.[29, 39]

The purpose of this paper is to cite the experience at Los Angeles Childrens Hospital as a means of reviewing the problems inherent in the treatment of patients with meningitis, and to assess the role of adrenocortical hormones in therapy. The problem of tuberculous meningitis (see p. 1225) has been excluded from this review.

PATHOGENESIS AND ETIOLOGY

Meningitis is usually secondary to bacteremia, but may occur by direct extension from a contiguous infection. The invading organism can be isolated from the nasopharynx and blood in 70 per cent of the cases. Direct invasion of the meninges occurs more often in patients with pneumococcal meningitis, for example, from otitis media, mastoiditis, and in other defects such as a skull fracture or cerebrospinal fluid otorrhea. The search for such associated lesions must be carefully carried out. Meningomyelocoele may be the portal of entry for pseudomonas, and neurosurgical wounds for staphylococci.

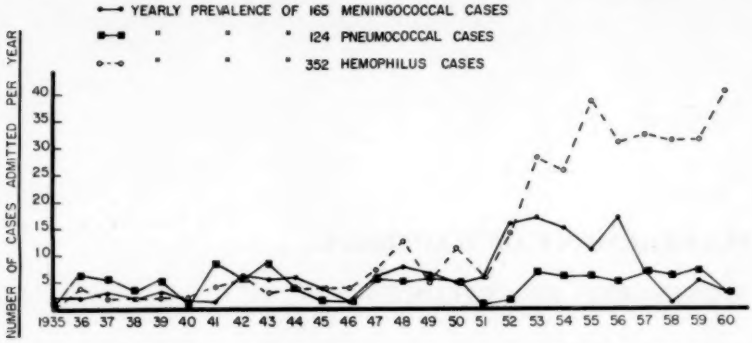
YEARLY PREVALENCE OF 165 MENINGOCOCCAL CASES
" " " 124 PNEUMOCOCCAL CASES
" " " 352 HEMOPHILUS CASES
NUMBER OF CASES ADMITTED PER YEAR
40
35
30
25
20
15
10
5
1935 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

Fig. 16. Yearly prevalence of meningococcal, pneumococcal and H. *influenzae* type B meningitis at the Childrens Hospital from 1935 to 1960.

The pneumococcus, meningococcus and *Hemophilus influenzae*, type B, account for 60 to 70 per cent of meningitis in children.[26, 46] Figure 16 shows their prevalence at the Childrens Hospital of Los Angeles from 1935 to 1960. During this 25-year period 352 cases of H. influenzal meningitis, 165 of meningococcal and 124 of pneumococcal were seen. The variable occurrence of meningococcal infection and the unchanging prevalence of pneumococcal infection are noteworthy. The larger number of cases caused by Hemophilus infection in recent years, on the other hand, is unexplained, since the total number of hospital patients admitted during these years has remained about the same (7000 to 9000 patients per annum).

Variable transfer of certain antibodies across the placenta and lag in the development of active immunity after birth are responsible for the relatively high incidence of meningitis in early infancy and help to explain the prevalence of certain unusual causative organisms. For example, antibody against *H. influenzae* is transferred readily, conferring protection for about three months. Coliform antibody, on the other hand, is transferred poorly, resulting in little protection.[16, 53]

DIAGNOSIS

The age of the patient at the time of onset is often helpful in arriving at the diagnosis. *Hemophilus influenzae*, pneumococcus and meningococcus rarely cause meningitis before six weeks of age. During the neonatal period, meningitis is likely to be caused by a coliform organism, occasionally by a staphylococcus and rarely by a streptococcus or listeria.

Male infants with meningitis outnumber female infants about 2:1. The sex distribution is unexplained (Fig. 17).

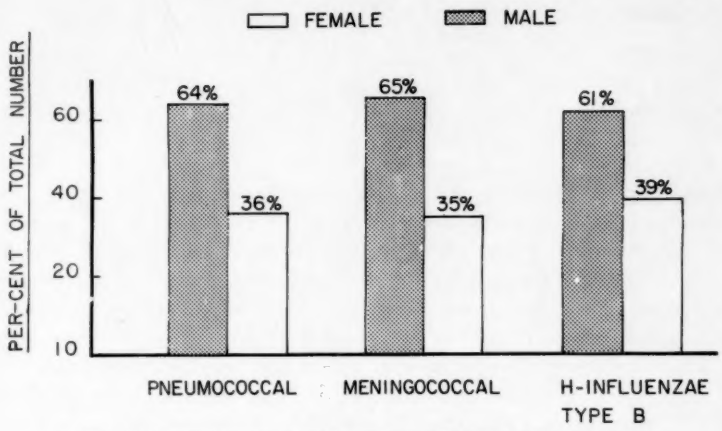

Fig. 17. Preponderance of male patients with purulent meningitis.

The clinical symptoms of meningitis in children are similar. A respiratory infection with or without otitis media often precedes the onset of meningitis by two or three days. Occasionally the onset is fulminating, as in the Waterhouse-Friderichsen syndrome, but here the nature and severity of the disease help to suggest the diagnosis. The occurrence of petechiae in our experience is almost pathognomonic of meningococcal infection. Only 3 of 352 patients with meningitis caused by *H. influenzae* and one of 124 patients with pneumococcal meningitis exhibited petechiae. This is in sharp contrast to meningococcal meningitis, which is accompanied by a petechial rash in 50 to 60 per cent of cases.[30] The rash at times may appear as an erythematous maculopapular lesion or with ecchymoses in severely ill patients.

The symptoms, physical findings, causative agents, treatment and prognosis are quite different in the neonate[25, 49] from those in the older child or adult. The classic symptoms of drowsiness, stiff neck, headache, vomiting, occasional convulsions and behavioral changes seen in the older child contrast with the subtle listlessness, poor feeding, irritability, respiratory distress and frequent convulsions in the infant. Although both age groups may have fever, it is not uncommon for the neonate with meningitis to have a normal or even subnormal temperature. He may be cyanotic or jaundiced, and his abdomen may be distended. Frequently the anterior fontanel is full or bulging. Positive Brudzinski and Kernig signs are usually present in the older child, but may be absent in the infant. Early diagnosis can be achieved only by a high index of suspicion and by examination of the cerebrospinal fluid of a young infant who has any of these symptoms or is "not doing well" for obscure reasons.

LABORATORY EXAMINATIONS

Examination of the cerebrospinal fluid will usually confirm the diagnosis of meningitis. Unless papilledema is present, enough fluid should be obtained for cell count, smear and culture, and for determination of protein and glucose content. These tests can be performed easily with 8 to 10 ml. of fluid. The chloride content of the cerebrospinal fluid in children is of little value. If papilledema is present, only a few drops for cell count and culture should be removed cautiously in order to avoid herniation of the brain stem into the foramen magnum. In our experience a smear for identification of the organism is of value, but may be misleading. Smears from 16 of our cases of *H. influenzae* meningitis were incorrectly interpreted as revealing gram-negative diplococci or gram-positive cocci. Addition of type-specific antiserum to bacteria suspected of being *H. influenzae* may cause visible capsular swelling (Quellung reaction). Fluorescent antibody techniques appear promising for rapid bacterial identification, but must await further clinical trial.

The cerebrospinal fluid cell count is usually elevated, with predominance of polymorphonuclear leukocytes, in contrast to the usual lymphocytic response seen in aseptic meningitis, tuberculous meningitis and tumors of the central nervous system.

The culture is the most important single laboratory procedure and must be performed on every cerebrospinal fluid specimen. A pathogenic organism is occasionally isolated from "clear" cerebrospinal fluid.

Protein is significantly elevated in almost all cases of untreated bacterial meningitis, but not as much in aseptic meningitis or brain tumor. Cerebrospinal fluid glucose is usually decreased in bacterial and tuberculous meningitis and occasionally in association with brain tumor or central nervous system leukemic infiltrates. It is rarely decreased in aseptic meningitis. Table 32 outlines the significant cerebrospinal fluid findings.

Cultures of blood and nasopharynx are also of value. Other sites of possible bacterial infection should also be cultured. Organisms can

TABLE 32. *Significant Cerebrospinal Fluid Findings in Various Pathologic States*

DISEASE	PREDOMINANT CELLS	SUGAR	PROTEIN
Bacterial meningitis	Polymorphonuclear	Decreased	Elevated
Partially treated meningitis	Lymphocytes	Normal or decreased	Elevated
Aseptic meningitis	Lymphocytes	Normal	Normal or elevated
Tuberculous meningitis	Lymphocytes	Decreased	Elevated
Brain abscess	None or lymphocytes	Normal	Elevated
Brain tumor	None or lymphocytes	Normal or decreased	Normal or elevated
Lead encephalitis	None or lymphocytes	Normal	Elevated

sometimes be recovered from these when they fail to grow from the cerebrospinal fluid. Antibiotic sensitivity studies are valuable for proper selection of antimicrobial agents effective against coliform organisms or staphylococci.

Tuberculous and occasionally other types of bacterial meningitis may cause loss of sodium and hyponatremic convulsions. Comatose patients, those with convulsions and patients receiving parenteral fluids for more than two or three days should have measurement of the serum sodium, potassium, chlorides and carbon dioxide. The routine laboratory procedures such as blood cell count, urinalysis and tuberculin skin test should also be performed. Occasionally roentgenographic views of the skull and an electroencephalogram are of value when subdural effusion is present.

TREATMENT

Bacterial meningitis should be considered a medical emergency. Specific antibiotic therapy is the pivot around which all other treatment revolves. Since the infecting organism often cannot be recognized immediately with certainty, antimicrobial agents must be selected against the most likely pathogens. Sulfadiazine, penicillin and chloramphenicol are the drugs of choice for H. influenzal, meningococcal and pneumococcal infections, respectively. All three drugs should be included in the initial treatment unless a specific bacterial diagnosis can be made immediately. As soon as the infecting organism has been identified, the choice of antibiotics can be modified appropriately (see Appendix).

In the neonatal age group a coliform or staphylococcal cause is more likely, and the choice of antibiotic should be modified accordingly. When antibiotic sensitivity studies of the offending organism are available, these may be used as a guide. In general, the most useful antibiotics in this age group are tetracycline or chloramphenicol, sulfadiazine and streptomycin. Penicillin is rarely of value. The dosages are outlined in the Appendix.

In order to ensure uninterrupted administration of antibiotics and appropriate intravenous fluids, a small polyethylene catheter should be inserted into a vein. Enough fluid and electrolytes should be given for normal maintenance and replacement of deficits resulting from anorexia and vomiting. Because of the danger of vomiting and aspiration, oral feeding should be withheld until the patient is fully alert and responsive.

Immediate expansion of the intravascular space by colloid solution is indicated in the presence of peripheral vascular collapse. Dextran may be used until plasma or, preferably, blood can be given. In the event that the blood pressure cannot be maintained with blood and other

fluids, levarterenol bitartrate, 4 mg. per 1000 cc. of solution, may be given *slowly* intravenously. Sometimes greater concentrations may be needed to maintain blood pressure. Such medication should be stopped as soon as the clinical status permits.

If the patient shows clinical signs of severe cerebral edema, urea,* 1 gm. per kilogram of body weight, may be given intravenously and repeated every 8 hours as needed. Urinary output must be carefully observed when urea is administered. Diuresis usually follows and heralds a decrease in cerebral edema. A significant prompt improvement in the clinical condition of several patients so treated has been noted. Hypothermia also may be helpful in selected patients, but the problems of fluid therapy, drug dosage and technical difficulties make its use hazardous.

Meningitis Caused by Hemophilus Influenzae, Type B

Excellent results have been reported by several authors using various antibiotic combinations. Shaw and Bruyn[45] and Meade and Weinstein[37] have demonstrated excellent results with streptomycin and sulfonamides, Alexander[1] and Smith[48] with chloramphenicol and sulfonamides, and Carson[6] and Moll[39] with the tetracyclines and sulfonamides. During the past 11 years 3 basic antibiotic regimens have been utilized at this institution. Until 1958 almost all patients received streptomycin in addition to sulfadiazine and either oxytetracycline, tetracycline or chloramphenicol. Streptomycin has been omitted since then without apparent effect on morbidity or mortality. The mortality rate in each group was as follows: oxytetracycline, 66 patients, 4.5: tetracycline, 105 patients, 8.4; chloramphenicol, 64 patients, 12.5 per cent. Unfortunately, these were not controlled observations, and the differences in mortality rate are not statistically significant (Fig. 18). Our experience would indicate that if the patient survives the first 24 to 36 hours of treatment, he will usually recover regardless of which of the 3 basic antibiotics is administered—oxytetracycline, tetracycline or chloramphenicol.

Damage to the central nervous system occurred in 17 (7.2 per cent). The most severely handicapped children were those under one year of age and those who had been ill two weeks or more before admission. All but three of the patients with permanent brain damage had convulsions during the course of their illness.

Subdural effusions were found in 32 (13.6 per cent). The subdural space of these patients was investigated because of persistent or recurrent fever (17), persistent irritability (7), "crack pot" sound on percus-

* U.S.P. Lyophilized urea made by Travenol Laboratories, Incorporated, Morten Grove, Illinois.

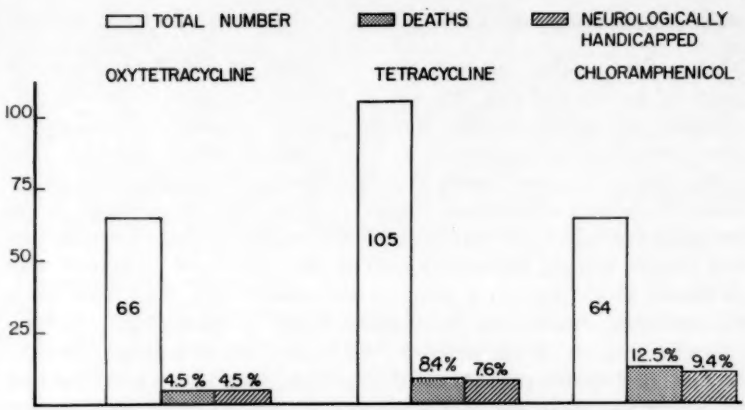

Fig. 18. Mortality and morbidity in 235 cases of *H. influenzae* meningitis in 3 treatment groups (oxytetracycline, 66; tetracycline, 105; chloramphenicol, 64). Results are not statistically significantly different ($X^2 = 6.3212$).

sion of the cranium (3), convulsions (3), and without special indication in two. No subdural effusion was discovered at autopsy. Therapy usually consisted in repeated tapping of the subdural space, but surgical exploration was necessary in 11 patients; membranes were found and removed in 6 of these. Three had no membrane or other significant findings. Adhesive arachnoiditis was found in one, and cystic degeneration of the brain in the other.

It was possible to follow up 23 of the 32 patients for a sufficient period to evaluate residual neurologic impairment. Eight were found to have significant brain damage as manifested by mental retardation in three, behavior disorders with slow school progress in two, sixth nerve palsy in one, spastic hemiplegia with mental impairment in one and hearing loss in one. This residual 25 per cent morbidity following subdural effusion, as has been pointed out,[40] does not necessarily indicate that the effusion caused the brain damage. Both may be related to the severity of the initial meningitis.

Nineteen deaths occurred in this series of 235 cases for an 8 per cent mortality rate. Fourteen of the 19 deaths were in children older than one year and were distributed rather evenly from one to 12 years of age. Thirteen of the 19 deaths occurred in children with fulminant disease, who expired rapidly in spite of all emergency efforts. Autopsy was performed in seventeen. In addition to the usual findings of profuse purulent exudate over the brain, five showed significant cerebral edema, four had fatty infiltration of the liver, and two showed massive bilateral adrenal hemorrhage. Acute staphylococcal enterocolitis occurred in one patient treated with oxytetracycline. In another child thrombosis of the sagittal and lateral venous sinuses was found.

Meningococcal Meningitis

Meningococcal infections may occur in epidemics, but they are usually endemic in the pediatric age group. During the period 1935–60, 165 patients with meningococcal meningitis were admitted, 22 of whom were immediately transferred to a contagious disease hospital. The initial symptoms were usually lethargy, fever and vomiting. The recognition of showers of petechial lesions served to alert the physician to the probable etiology in 60 per cent of the patients. The clinical course was usually benign, but occasionally it was rapid and fulminant with profound shock, extensive purpura and death in a matter of hours (Waterhouse-Friderichsen syndrome). Blood pressure was a helpful prognostic sign.[30] In our patients with systolic blood pressure less than 60 mm. of mercury at the time of admission, mortality was 60 per cent in comparison to 10 per cent in those with normal blood pressure. Endophthalmitis, pericarditis and joint infection were rarely encountered.

Sulfadiazine was the drug of choice for therapy. Most clinicians added penicillin to the therapeutic regimen, but the evidence that this improved survival was not impressive. Prophylactic sulfadiazine was given to all family contacts.[32]

Five patients suffered residual neurologic damage. Subdural effusion was uncommon, occurring in only eight, seven of whom recovered completely. In the series of 165 cases, 22 deaths occurred, an over-all mortality of 15.4 per cent (Fig. 19). Six of these patients died so quickly

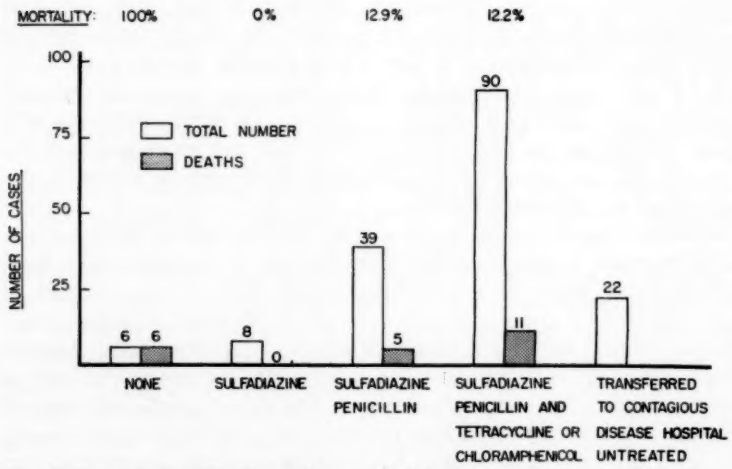

Fig. 19. Relation of antibacterial therapy to mortality in 165 cases of meningococcal infection.

that no antibacterial medications were administered; one expired from an intercurrent diarrhea. Fifteen of the 22 presented a clinical and pathologic picture compatible with the Waterhous-Friderichsen syndrome. The use of corticosteroids did not appear to alter the mortality. Before 1953, six of seven patients with the clinical diagnosis of this syndrome died. Since 1953 eleven such children were seen, and two survived. All of the latter group received intravenous hydrocortisone in the usual therapeutic dosage.

Pneumococcal Meningitis

During the period 1935–60, 124 patients with this disease were admitted. Only seven of 45 patients survived before penicillin was available. In accord with others,[20, 43, 51] we have observed remarkable subsequent improvement in survival. Initially, when penicillin was given intrathecally, the morbidity rate was high. Figure 20 reveals that 41 per cent of the 17 survivors treated with intrathecal penicillin suffered severe neurologic damage. Even when this method of penicillin administration was abandoned, the occurrence of neurologic damage was still 31 per cent, although mortality dropped to 7 per cent. When large amounts of penicillin were given parenterally as recommended by Alexander,[1] mortality declined even further to 2 per cent with a neurologic sequelae rate of 21 per cent (Fig. 20). In our experience the intrathecal use of penicillin is unwarranted.

Even though penicillin was effective, the occurrence of complications remained high because of the large number of cases in infants less than one year of age (Fig. 21). Mastoiditis and purulent otitis media occurred frequently and at times delayed accurate diagnosis. In addi-

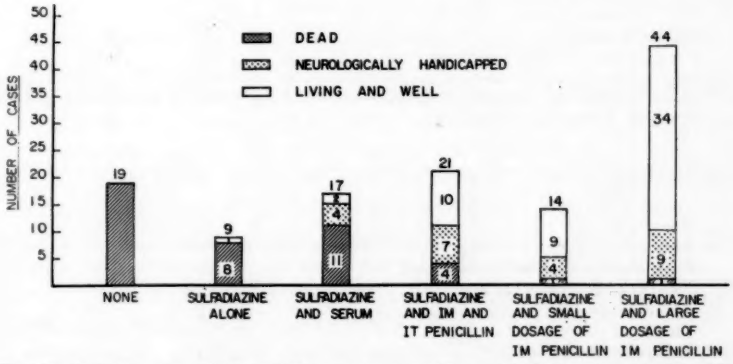

Fig. 20. Relation of antibacterial therapy to mortality, morbidity and survival in 124 cases of pneumococcal meningitis.

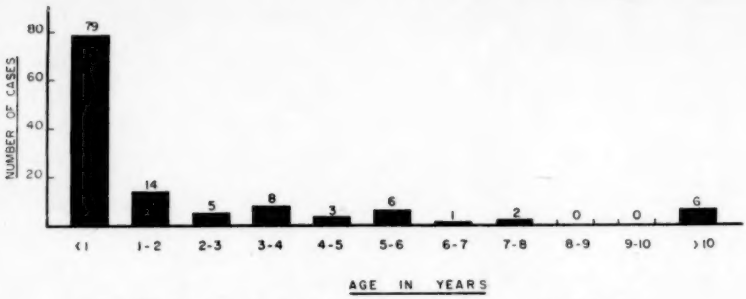

Fig. 21. Age prevalence in 124 cases of pneumococcal meningitis.

tion, predisposing, underlying conditions (Table 33) frequently complicated the clinical course. The occurrence of hematologic disorders, congenital anomalies and head injuries is notable. Four patients with hematologic disorders predisposing to infection[42] and one with cirrhosis of the liver also had undergone prior splenectomy. Associated hematologic disorders included sickle cell disease (3), hypoplastic anemia (1), Aldrich-Dee syndrome (3), severe iron deficiency anemia (4), Cooley's anemia (1) and megaloblastic anemia of infancy (1).

The neurologic handicaps suffered by these patients were generally severe. Table 34 reveals that 13 are mentally defective, 10 are deaf, 2

TABLE 33. *Predisposing Underlying Conditions in 124 Cases of Pneumococcal Meningitis*

Hematologic disorders	13
Congenital anomalies	8
Postsplenectomy*	5
Nasal fibroma	1
Head injury	4
Mastoiditis	30
Otitis media, purulent	72

* Some patients had more than one associated finding. Four of the 5 splenectomized patients had hematologic disorders.

TABLE 34. *Neurologic Handicaps in 81 Surviving Children with Pneumococcal Meningitis*

HANDICAP	NUMBER OF CASES
Mental retardation (3 also deaf)	13
Deaf (not retarded)	7
Seizure disorder	1
Cerebral palsy	2
Behavior disorder	1
Speech defect	1
Precocious puberty	1
Total	26

have cerebral palsy, one has a seizure disorder, one is a behavior problem, and one has a speech defect. Deafness was much more common in pneumococcal meningitis than with either meningococcal or *H. influenzae*, type B, meningitis.

Mastoidectomy was performed in 19 of the 30 patients with roentgenographic evidence of mastoiditis. Operation was generally delayed until the patient's clinical condition was well stabilized. There were no fatalities in this group as the result of the surgical procedures.

Subdural effusion occurred in only seven patients. Three of these responded to simple repeated tapping of the subdural space, and four required craniotomy and removal of the membrane.

Clinical relapse occurred in four patients. Two of these received grossly inadequate penicillin therapy as judged by present standards. One patient had five separate episodes of meningitis associated with persistent cerebrospinal fluid otorrhea. One splenectomized patient relapsed after 11 days of therapy with both penicillin and sulfadiazine.

Two patients had a fulminating course consistent with Waterhouse-Friderichsen syndrome. Corticosteroids were administered to both without avail. Two other severely ill patients received corticosteroids in an attempt to reduce the inflammatory reaction, and it was the clinical impression that both were benefited.

Staphylococcal Meningitis

Staphylococcal meningitis can develop in any age group, although as a primary disease it tends to be more prevalent in the neonatal period. In six out of 11 cases meningitis was secondary to neurosurgical procedures such as ventriculocardiac shunts. Such lesions as pustules elsewhere on the body should arouse suspicion of this type of meningitis, so that an effective antistaphylococcal drug may be included in the initial treatment.

Therapy was guided by antibiotic sensitivity testing and consisted of at least two drugs which diffuse into the cerebrospinal fluid in adequate concentration and to which the bacteria were sensitive.

The most useful drugs were erythromycin, chloramphenicol and bacitracin, although tetracycline and penicillin G were used if the organism was sensitive. These drugs were required in full dosage parenterally until satisfactory clinical response was achieved. Treatment was usually continued for at least three weeks, and occasionally longer, depending upon the patient's clinical condition.

Drugs such as ristocetin and vancomycin[50] had limited value because of their failure to cross the meninges. This was well demonstrated by the relapse of one patient receiving ristocetin after almost complete clearing of the cerebrospinal fluid on chloramphenicol. At the time of

relapse, the cerebrospinal fluid ristocetin content was zero. We have had little experience with Staphcillin.

With appropriate treatment as outlined in the Appendix, most patients diagnosed and treated early should survive. The danger of relapse is great, however, especially in those with neurosurgical shunts. The two patients failing to survive in this group of 11 were hospitalized for less than 20 hours. One, however, had been admitted repeatedly for recurrent meningeal infection associated with a ventriculocardiac shunt.

Coliform Organisms

In our experience *Escherichia coli* and paracolon organisms have been relatively frequent causes of meningitis during the neonatal period. Twenty-one of the 29 infections occurred in infants under one month of age. Three others were in infants between one and two months of age. Two cases followed neurosurgical procedures, and the other three were in infants, none of whom were over eight months old.

It is noteworthy that in this group of patients the referring physicians failed to recognize the clinical signs of meningitis in the very young. These infants were ill from a few hours to as long as 42 days before admission, with an average length of illness of 8 days. Many had received antibiotics before admission.

Symptoms and signs in order of declining frequency were listlessness, fever, convulsions, cyanosis, respiratory distress, vomiting, poor feeding, irritability, jaundice, bulging fontanel, hypothermia, abdominal distention, and diarrhea. Singularly absent were the cardinal meningeal signs found in older infants and children.

Most of the organisms were sensitive to the tetracyclines, chloramphenicol and streptomycin. Although sensitivity testing for sulfonamides is not ordinarily performed, these drugs were clinically effective against coliform organisms. Since sulfasoxizole may be associated with development of kernicterus in premature infants, sulfadiazine was selected for therapy in these patients. Chloramphenicol, tetracycline and streptomycin were all effective. Chloramphenicol,[21] however, has been shown to be toxic to newborn infants and especially to prematures in the usual doses. For this reason, tetracycline, which does not have a cumulative effect (unpublished data of P. Dohi, R. Koch and L. D. Asay), was selected for treatment in most cases.

Relapses did occur in two patients whose treatment was stopped too early. It is our feeling that therapy should be continued for at least two weeks and until the cerebrospinal fluid cell count is below 50.

The mortality rate was high (55 per cent). Only 16 patients were cured, and three of these were left with severe neurologic handicaps.

Pseudomonas and Other Gram-Negative Organisms

Gram-negative bacilli such as achromobacter, flavobacterium and pseudomonas, formerly thought to be nonpathogenic, are now known to cause meningitis in infancy.[5, 15] Pseudomonas infections of all types have become more common during the past few years.[3] Four of the 10 cases of pseudomonas meningitis recorded from 1950 to 1959 developed during the year 1959. Almost all these patients suffered from another primary disease. Six had meningomyeloceles, one eczema vaccinatum, one mastoiditis, and two were premature infants.

The most useful antibiotics were streptomycin, oxytetracycline, tetracycline and polymyxin B. Because of the failure of the last named to cross the meninges in adequate concentrations,* it has been necessary to utilize intrathecal administration. Mortality rate has been 50 per cent. Colymycin* may prove useful, but experience so far is limited.

Salmonella

Salmonella organisms cause a most distressing, but fortunately infrequent, type of meningitis. Smith[47] reviewed the literature and added 6 cases seen at this hospital from 1944 through 1953. Three patients recovered, one with residual mental retardation and blindness. Three more patients have been seen since 1953. Two were neonates, and one had hypogammaglobulinemia with chronic salmonellosis. All expired, one within 24 hours and the other two after prolonged therapy with multiple antibiotics.

In view of the high mortality rate, it seems essential that immediate intensive antibiotic therapy with bactericidal drugs be administered whenever this agent is identified in the cerebrospinal fluid. It is recommended that streptomycin, chloramphenicol, sulfadiazine and colymycin be given parenterally in maximum dose until sensitivity studies in vitro are available. If the patient does not do well, polymyxin B should be administered intrathecally or intraventricularly in case of an intraspinal block. Polymyxin caused a transient paralysis in one neonate when a dose of 1 mg. was used intrathecally. This method has proved successful for treating pseudomonas meningitis and may well be useful for salmonella.

Listeria Monocytogenes

This is an easily grown, somewhat pleomorphic, motile, gram-positive rod which forms small, round colonies surrounded by a zone of beta hemolysis on blood agar. It tends to infest birds and animals and causes

* Unpublished data of A. Lee, R. Koch and L. D. Asay.

only an occasional infection in human beings. It has been associated with habitual abortion and neonatal meningitis.[22]

Two cases of Listeria meningitis were seen in newborn infants. The organisms were sensitive in vitro to tetracycline, and the infections responded promptly to therapy. Treatment of experimental infections in animals also indicates that tetracycline is the drug of choice.[44]

The Role of Corticosteroids*

Opinions differ considerably about the role of corticosteroid therapy in the treatment of severe infections. This has resulted from the appearance of many contradictory reports of success or failure of treatment with adrenal corticosteroids, and from the lack of consistent criteria for their use.

In the treatment of meningococcal infections, the prevention of the Waterhouse-Friderichsen syndrome[17, 60] has been the primary motivation for the administration of corticosteroids. The fulminant clinical course accompanied by peripheral vascular shock has been considered secondary to adrenal insufficiency, usually from bilateral adrenal hemorrhage. The recovery of some patients after steroid administration supported the hypothesis that the patient might be deficient in adrenal steroids.[2, 23] On the other hand, many authors reported failure of corticosteroids in the treatment of shock.[7, 34, 35, 45, 57, 58] In a controlled study of 56 patients, Lepper and Spies[34] found no difference in outcome between patients who received intravenous hydrocortisone and a similar group who did not receive corticosteroids. Further, hydrocortisone was given to the only five patients who died, all with bilateral adrenal hemorrhage. Others[12, 14] have observed that the Waterhouse-Friderichsen syndrome is not necessarily accompanied by adrenal hemorrhage or destruction. Moreover, *increased* blood corticoid levels have been demonstrated in patients with severe infection, including those with meningococcemia and the Waterhouse-Friderichsen syndrome.[27, 28, 38] In patients with severe infection and shock, intravenous ACTH elicited a further increase in plasma cortisone levels.[38] Occasionally, low levels of blood corticoids were found in infants dying of this infection.[27, 28] May[36] has suggested that the effect of the endotoxin of the bacterial organism on body cells other than those of the adrenals is the primary factor. The pathogenesis of shock in the Waterhouse-Friderichsen syndrome is uncertain, but the available evidence suggests that adrenal insufficiency is not usually a factor.

Difficulties in assessing the effect of corticosteroids have been the lack of a consistent definition of the Waterhouse-Friderichsen syndrome and the scarcity of well controlled studies. The term "Water-

* The term "corticosteroids" is used to indicate cortisone or its analogs, including synthesized steroids not occurring naturally.

house-Friderichsen syndrome" should be restricted to the clinical state manifested by overwhelming sepsis, peripheral vascular shock and the finding of bilateral adrenal hemorrhage at necropsy. The term "fulminant meningococcemia" should be used for those cases with vascular collapse and severe hemorrhagic lesions without adrenal pathology.[33] By defining terms, perhaps more suitable criteria for the evaluation of the use of corticosteroids will result.

Corticosteroids have been suggested for all patients with meningococcal infections to prevent cardiovascular collapse.[7, 23] May,[36] in contrast, has indicated that steroids may be harmful to the patient with meningococcemia. Because of the similarity of the effects of meningococcal endotoxin to those seen in the Shwartzman phenomenon,[8, 55] it has been suggested that corticosteroids may actually precipitate the Waterhouse-Friderichsen syndrome. This has also been suggested from clinical observations. Margaretten and McAdams[35] reported three fatal cases of meningococcemia in patients with autopsy findings of renal cortical necrosis who had received adrenal cortical extract or hydrocortisone. The lesions resembled those seen in the Shwartzman reaction. Experimental evidence in favor of the use of corticosteroids has been offered by Melby[28] and Spink.[52] They suggest that the endogenous production of cortisol with acute infection, even though increased above resting, is inadequate to combat the factors responsible for tissue damage and circulatory collapse. The administration of endotoxin to dogs caused shock despite elevated plasma cortisol. The administration of hydrocortisone to the animals, however, prolonged life, lessened gastrointestinal hemorrhage, and reduced previously elevated serum glutamine-oxalacetic transaminase (SGOT) levels. The SGOT level was taken as an index of tissue destruction. It was felt that if corticosteroids are used, large amounts should be given.[38, 52]

In addition to their use in cases of bacterial shock, corticosteroids have been introduced into the treatment of bacterial meningitis as anti-inflammatory agents. When it was found that ACTH and cortisone could inhibit the growth of fibroblasts and the formation of granulation tissue,[4, 54, 56] it became apparent that they might be of value when used in conjunction with antibiotics in the treatment of meningitis. Residual neurologic damage from meningitis seemed proportional to the extent of the inflammatory reaction, despite the use of antimicrobial agents which resulted in disappearance of the infecting organisms. If the inflammatory exudate could be suppressed, a consequent decrease in the amount of granulation tissue was expected to decrease mortality and morbidity. In tuberculous meningitis, analogous in abnormal central nervous system findings to those of pneumococcal meningitis, corticosteroids are generally recognized as valuable adjuncts to chemotherapy.[9, 10, 59] Moreover, the salutary effects of corticosteroids are more striking when the cerebrospinal fluid pressure is elevated or a

block to free flow exists.[59] The beneficial effects of corticosteroids in tuberculous meningitis may be due to reduced formation of fibroblasts and resolution of exudate.[4, 13, 24, 54, 56, 59]

In pneumococcal meningitis, as in tuberculosis, the effects of granulation tissue may be severely unfavorable, and corticosteroids might be expected to be beneficial. In one series of 12 adult patients, all treated with antibiotics and ACTH (four received hydrocortisone or cortisone in addition), one death and no unfavorable sequelae occurred.[41] The study was not controlled, however, and most of the patients were hospitalized and treated within two days of the onset of illness. In another series of 23 patients in which alternate patients were treated with hydrocortisone, no difference was evident between the group that received antibiotics alone and the group that received hydrocortisone in addition to antibiotics.[34]

We have administered corticosteroids to a few patients with pneumococcal meningitis and have been favorably impressed with the results. No deaths or apparent neurologic sequelae have occurred.

In *H. influenzae* meningitis, Lepper and Spies[34] found no difference in mortality in 57 patients alternately treated with or without hydrocortisone and ACTH. In addition, 25 per cent of their steroid-treated patients had subdural effusions, compared to 3 per cent of the group that did not receive steroids. This difference was considered to be significant. In the few patients with *H. influenzae* meningitis to whom we have administered corticosteroids because of increased intracranial pressure, we have not observed convincing beneficial effects.

From published data and our own experience it is difficult to make recommendations for the use of corticosteroids in meningitis. They appear to have a beneficial effect in tuberculous meningitis and may also benefit selected patients with pneumococcal meningitis. They do not appear to benefit patients with *H. influenzae* or meningococcal meningitis, and may even be harmful.

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APPENDIX

Guide for Treatment of Acute Bacterial Meningitis

I. Unknown Etiology—3 drugs:

1. *Penicillin, aqueous:* 600,000 units every 4 hours intramuscularly, or 2,000,000 to 4,000,000 units per day, intravenously.

2. *Sulfadiazine:* 40 mg. per kilogram stat, intravenously; then 200 mg. per kilogram daily, intravenously, orally or by clysis. Avoid intravenous administration unless patient is in shock.

   NOTE: Maximum dose is 6 gm. per day. Check urinalysis daily and blood cell count regularly twice weekly. For newborns use 75 mg. per kilogram daily.

3. Patients may be treated with either

   Chloramphenicol: 50 mg. per kilogram stat, intravenously; then 100 mg. per kilogram daily, intravenously or intramuscularly.

   NOTE: Maximum dose is 4 gm. per day. Check blood cell count 3 times weekly. For neonates or prematures use 25 mg. per kilogram daily, intramuscularly in 2 equally divided doses.

   or

   Tetracycline: 50 mg. per kilogram daily, intravenously by cutdown, changing to oral administration when patient is improving and taking fluids well by mouth. Avoid intramuscular use.

Treatment should be continued for at least 7 days after patient has become afebrile. Utilize oral administration when it is tolerated.

II. MENINGOCOCCUS:

1. *Sulfadiazine:* Same as for unknown. If patient is severely ill, add

   Penicillin: Same as for unknown.

Continue treatment for 5 afebrile days.

Prophylaxis for immediate contacts:

A single dose of 2 gm. of sulfadiazine orally is sufficient for adults. For children give 30 to 40 mg. per kilogram in a single dose.

III. HEMOPHILUS INFLUENZAE, TYPE B:

1. *Sulfadiazine:* Same as for unknown.
2. Patients may be treated with either

   Chloramphenicol: Same as for unknown.

   or

   Tetracycline: Same as for unknown.

3. *Streptomycin:* If patient is severely ill, in dosage of 50 mg. per kilogram daily, intramuscularly, in divided doses every 6 to 12 hours. Maximum, 1 gm.

Continue treatment for 7 afebrile days.

IV. PNEUMOCOCCUS:

1. *Penicillin, aqueous:* 2 to 20 million units daily, intravenously.
2. *Sulfadiazine:* Same as for unknown.

Continue penicillin therapy for 3 weeks. Dosage may be reduced after 3 to 5 afebrile days to procaine penicillin, 600,000 to 1,000,000 units every 12 hours, intramuscularly. If course is relatively benign, patient may be treated with oral penicillin V or alpha phenoxyethyl penicillin after spinal fluid has cleared.

V. STAPHYLOCOCCUS—minimum of 2 drugs:

1. *Bacitracin:* 1000 units per kilogram daily. Progressively reduce dose as cells or albumin or sugar appears in urine.

2. *Chloramphenicol:* 100 mg. per kilogram daily, intravenously or intramuscularly or orally.

   or

   Erythromycin: 50 mg. per kilogram intravenously or orally.

   Treat for a minimum of 3 weeks.

VI. Coliform Organisms:

1. *Tetracycline* or *Chloramphenicol:* Same as for unknown. Tetracycline is preferred if infant is premature or newborn.
2. *Streptomycin:* 50 mg. per kilogram daily, intramuscularly. Maximum, 1 gm. daily.
3. *Sulfadiazine:* Same as for unknown.

   Treat for minimum of 3 weeks with 2 of the above-named drugs.

VII. Pseudomonas—3 drugs:

1. *Colymycin:* 5.0 mg./kg./day.

   or

   Polymyxin: 2.5 mg./kg./day, intramuscularly. Give polymyxin, 1 to 2 mg. daily, intrathecally, until cerebrospinal fluid is sterile. Intraventricular medication may be used if intrathecal administration is impractical.
2. *Streptomycin:* 50 mg. per kilogram daily, intramuscularly.
3. *Oxytetracycline:* 50 mg. per kilogram daily, intravenously.

VIII. Salmonella—minimum of 3 drugs:

1. *Tetracycline:* Same as for unknown.
2. *Chloramphenicol:* Same as for unknown.
3. *Streptomycin:* 50 mg. per kilogram daily, intramuscularly.
4. *Polymyxin* Intramuscularly and intrathecally. Should be considered if patient is critically ill or is failing to respond.

   Treat for at least 3 weeks and until spinal fluid is clear.

IX. Listeria Monocytogenes:

Tetracycline: Same as for unknown.

Treatment of Shock:

1. Serum electrolytes: carbon dioxide, sodium, potassium, chloride.
2. Plasma or whole blood intravenously as indicated.
3. Levarterenol, 4 mg. per 1000 cc., or Neo-Synephrine. Give slowly, titrating blood pressure when other measures fail.
4. Hydrocortisone, 10 to 15 mg. per kilogram (150 mg. per square meter) daily, intravenously, if patient fails to respond to foregoing measures. This is of doubtful value and may be contraindicated.

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ANTIMICROBIAL THERAPY IN RESPIRATORY TRACT DISEASES

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Indications for antimicrobial therapy in disease of the respiratory tract are rarely clear-cut. The pediatrician is constantly plagued by the decision "to treat or not to treat." An antimicrobial drug which may be lifesaving for an infant with severe bacterial pneumonia may be worthless or even harmful for a child with a viral infection.

Two decades ago the choice of an antibacterial drug was a simple task. In 1940 only sulfonamides were available. Today more than 15 antimicrobial agents have been added to the formulary. The selection of the appropriate drug for the treatment of an infection requires both clinical acumen and a knowledge of the virtues, limitations and hazards of the various antimicrobial agents.

FACTORS AFFECTING CHOICE OF ANTIBIOTICS

Figure 22 lists the various factors which may affect the selection of a particular antibiotic.

Clinical Impression of Etiology

Information derived from a careful history and physical examination will enable a physician to classify a respiratory illness into one of the syndromes listed in Table 35. Each syndrome may be caused by a variety of etiologic agents, most commonly bacterial or viral. Rickettsial, parasitic and mycotic respiratory diseases are relatively uncommon.

A knowledge of the most probable causative agent of each syndrome is helpful in assessing the clinical estimate of the etiology. For example, a clinical diagnosis of acute vesicular or ulcerative tonsillopharyngitis would suggest a viral etiology, most probably herpes simplex or Cox-

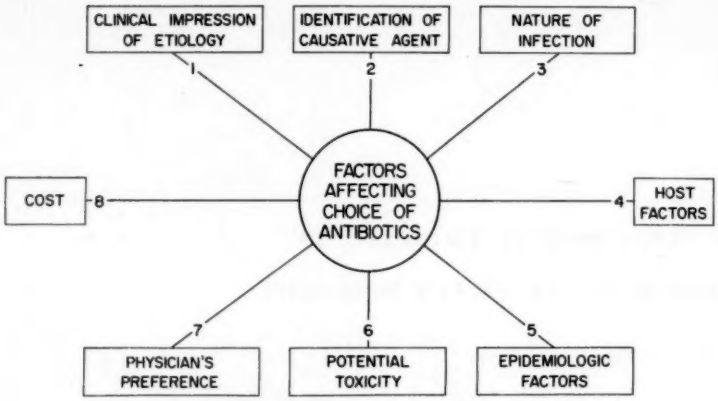


Fig. 22. Factors affecting the choice of an antibiotic.

sackie A virus. These infections are not affected by antimicrobial therapy. On the other hand, a diagnosis of acute exudative tonsillopharyngitis suggests a streptococcal etiology.

Identification of Causative Agent

The clinical estimate of the etiology may be confirmed or altered by the results of bacteriologic cultures. In acute exudative tonsillitis the identification of group A hemolytic streptococci on throat culture is confirmatory. Occasionally the results of the throat culture and failure to respond to penicillin therapy may suggest another etiology. For example, *Hemophilus influenzae* tonsillitis or viral tonsillitis will not be affected by penicillin therapy.

Nature of the Infection

The kind of respiratory infection will affect the decision to withhold or initiate antimicrobial therapy. For example, most cases of acute nasopharyngitis and acute bronchiolitis have a viral etiology. In view of the benign nature of *upper* respiratory tract infections, initial therapy with antibiotics is rarely indicated. On the other hand, acute bronchiolitis carries a serious prognosis and often resembles severe bacterial bronchopneumonia. Consequently a physician would be justified in initiating antimicrobial therapy for this "nonbacterial" disease. Subsequently the treatment may be discontinued if the clinical course and bacteriologic reports rule out a bacterial etiology.

TABLE 35. *Classification of Acute Respiratory Infections in Children by Clinical Syndrome and Etiologic Agent**

CLINICAL SYNDROMES	ETIOLOGY	
	Bacterial	Viral
Common cold, febrile nasopharyngitis, acute respiratory disease, acute catarrhal tonsillopharyngitis with or without conjunctivitis	Hemolytic streptococcus (in infants)	Adenovirus Eaton-Liu (PAP) Parainfluenza 3 (HA-1) Respiratory syncytial (RS) ECHO 8, 20, 28 Coxsackie A
Acute tonsillopharyngitis (exudative or membranous)	Hemolytic streptococcus† Corynebacterium diphtheriae	Infectious mononucleosis‡ Adenovirus
Acute tonsillopharyngitis (vesicular or ulcerative)		Herpes simplex† Coxsackie A†
Acute epiglottitis (croup)	Hemophilus influenzae, type B†	?
Acute laryngotracheitis with or without bronchitis (croup)	C. diphtheriae H. influenzae	Parainfluenza 1 (HA-2)† Adenovirus Parainfluenza 2 (CA) Influenza A Respiratory syncytial (RS) ECHO 11 Parainfluenza 3 (HA-1)
Acute bronchiolitis	H. influenzae ?	Adenovirus Parainfluenza 3 (HA-1) Eaton-Liu (PAP) Respiratory syncytial (RS)†
Acute pneumonitis	Pneumococcus† Staphylococcus Hemolytic streptococcus H. influenzae	Adenovirus Chickenpox Eaton-Liu (PAP) Influenza Measles Parainfluenza 3 (HA-1) Respiratory syncytial (RS)† Psittacosis

* Rickettsial, parasitic and mycotic infections are not included in this table.
† One of the most common etiologic agents.
‡ Viral etiology not proved.
PAP: primary atypical pneumonia.
CA: croup-associated.
HA: hemadsorption.
Modified from S. Krugman and R. Ward: *Infectious Diseases of Children.* 2nd ed. St Louis, C. V. Mosby Company.

Host Factors

A variety of host factors may influence the choice of a particular antimicrobial drug. A patient may be allergic to the drug of choice. In this event the second best drug would be selected. Other host factors such as age or the presence of another disease, e.g. rheumatic fever, would affect the selection of an antibiotic.

Epidemiologic Factors

The estimate of the etiology of the respiratory syndrome will be influenced by the knowledge of an epidemic of a particular bacterial or viral infection in the community. A nonexudative tonsillopharyngitis usually has a viral etiology. In the presence of an epidemic of scarlet fever the likelihood of a streptococcal etiology would increase. Under these circumstances penicillin therapy would be indicated.

Potential Toxicity

This factor is particularly important in situations which require the parenteral use of drugs such as bacitracin or neomycin. The virtues of these agents must be balanced against their nephrotoxic and ototoxic potentialities.

Physician's Preference

Past personal experiences have a profound effect on a physician's choice of an antimicrobial agent. The unfortunate occurrence of a severe toxic reaction or a fatal anaphylactoid episode may prejudice a physician against a particular drug.

Cost

The factor of cost may influence the choice of a sulfonamide in preference to a more expensive tetracycline preparation.

ANTIMICROBIAL THERAPY OF SPECIFIC RESPIRATORY SYNDROMES

Common Cold, Febrile Nasopharyngitis, Acute Respiratory Disease, and Acute Catarrhal Tonsillopharyngitis with or without Conjunctivitis

These four respiratory syndromes are most commonly identified as "upper respiratory tract infections." They are characterized by varying degrees of one or more of the following manifestions: nasal congestion and discharge, conjunctivitis, sore throat, cough, and tonsillopharyngeal

reddening without exudate. As indicated in Table 35, these infections usually have a viral etiology. Adenovirus, parainfluenza, PAP, respiratory syncytial (RS), ECHO and Coxsackie viruses have been associated with these diseases.[1, 2, 4, 6, 7, 11, 14] As newer respiratory viruses are identified, this list will increase.

This clinical syndrome is rarely caused by bacteria.[5] Rarely the hemolytic streptococcus may be responsible for nasopharyngitis in infants.[12]

ANTIMICROBIAL THERAPY. Antibiotics are not indicated for most upper respiratory tract infections of children; their use has neither therapeutic nor prophylactic efficacy. If a streptococcal etiology is suggested because of a known contact or a positive culture, penicillin therapy would be indicated.

Acute Tonsillopharyngitis with Exudate or Membrane

The group A hemolytic streptococcus is the most common cause of this disease, which is characterized by fever, sore throat and an exudative or membranous tonsillopharyngitis. Diphtheria and infectious mononucleosis are less common causes.

ANTIMICROBIAL THERAPY. The drug of choice is unquestionably penicillin. Optimum therapy may be achieved with any one of the following schedules:

1. Aqueous procaine penicillin, 600,000 units intramuscularly, daily for 10 days. (This regimen is not recommended because of the large number of injections.)
2. Benzathine penicillin G, 600,000 units intramuscularly as a single injection. (The disadvantage of this regimen is the high incidence of severe local reactions.)
3. Oral penicillin G or V, 300,000 units 4 times daily for 10 days. (Penicillin G should be given on an empty stomach.)
4. Various combinations of 1 and 3, such as intramuscular therapy for 3 days and oral administration for 7 days.

The regimen of penicillin therapy should be individualized. An effective, well tolerated and relatively inexpensive preparation is available as a mixture of 600,000 units of aqueous procaine penicillin and 600,000 units of benzathine penicillin G in a 2-ml. vial for intramuscular inoculation.[8] As indicated in Figure 23, a single injection provides an adequate antistreptococcal blood level for at least 10 days.

Erythromycin is an effective substitute for the treatment of patients allergic to penicillin. The recommended dose is 20 mg. per pound of body weight per day (4 times daily) for a 10-day period.

Sulfonamides are effective for prophylaxis but not treatment of streptococcal infections.

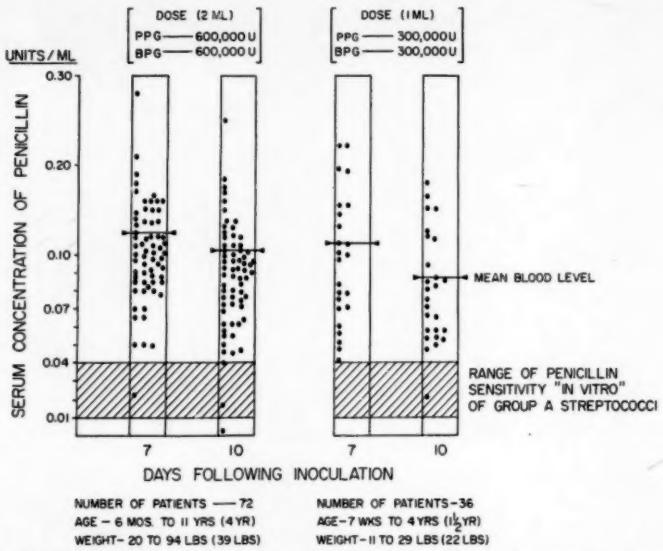


Fig. 23. Penicillin blood levels 7 and 10 days after a single injection of a mixture of aqueous procaine penicillin G (PPG) and benzathine penicillin G (BPG). Each black dot represents 1 blood level determination. (From S. Krugman and R. Ward: *Infectious Diseases of Children*, 2nd ed. C. V. Mosby Company.)

Acute Tonsillopharyngitis—Vesicular or Ulcerative

The syndrome of fever, sore throat and vesicles or shallow 2- to 4-mm. ulcers is usually caused by Coxsackie A or herpes simplex virus.[6, 13]

Antimicrobial therapy has no effect on the natural course of these infections.

Acute Epiglottitis

The syndrome of fever, barking cough, respiratory distress with inspiratory stridor, suprasternal retractions and a beefy, red, swollen epiglottis is most often caused by *H. influenzae*, type B. Other bacterial and viral agents are less common causes.

Antimicrobial Therapy. The drug of choice is either chloramphenicol or streptomycin. Our preference is chloramphenicol. In other clinics streptomycin may be preferred. It has been our practice to add a sulfonamide to the therapy. The following dosages are recommended: (*a*) chloramphenicol, 100 mg. per kilogram of body weight per day by mouth or intramuscularly; (*b*) sulfisoxazole or sulfadiazine, 150 mg. per kilogram of body weight per day by mouth. If streptomycin is used, the usual dose is 40 mg. per kilogram of body weight per day.

Acute Laryngotracheitis with or without Bronchitis

The clinical manifestations of this syndrome closely resemble those of acute epiglottitis. The obstruction, however, is more apt to be subglottic than supraglottic. As indicated in Table 35, acute laryngotracheitis is usually caused by one of many viral agents, most commonly Myxovirus parainfluenzae, type 1.

ANTIMICROBIAL THERAPY. It is difficult to make a clinical differentiation between bacterial and viral causes of laryngotracheobronchitis. In view of the poor prognosis associated with this disease and the importance of early, optimum therapy, it has been our practice to treat with antimicrobials until we can be certain that we are not dealing with a bacterial infection. Our regimen of therapy has included both penicillin and chloramphenicol.

Acute Bronchiolitis

This syndrome is seen most often in infants below the age of 18 months. The illness usually begins with an upper respiratory tract infection which progresses rapidly to severe cough, respiratory distress, retraction of the intercostal spaces, cyanosis and prostration. The respirations are rapid (about 60 per minute), shallow, labored and accompanied by wheezing. The physical findings and roentgenogram are compatible with the picture of obstructive emphysema; e.g. hyperresonant percussion note, prolonged expiration, and abnormally transparent lung field with depressed diaphragms.

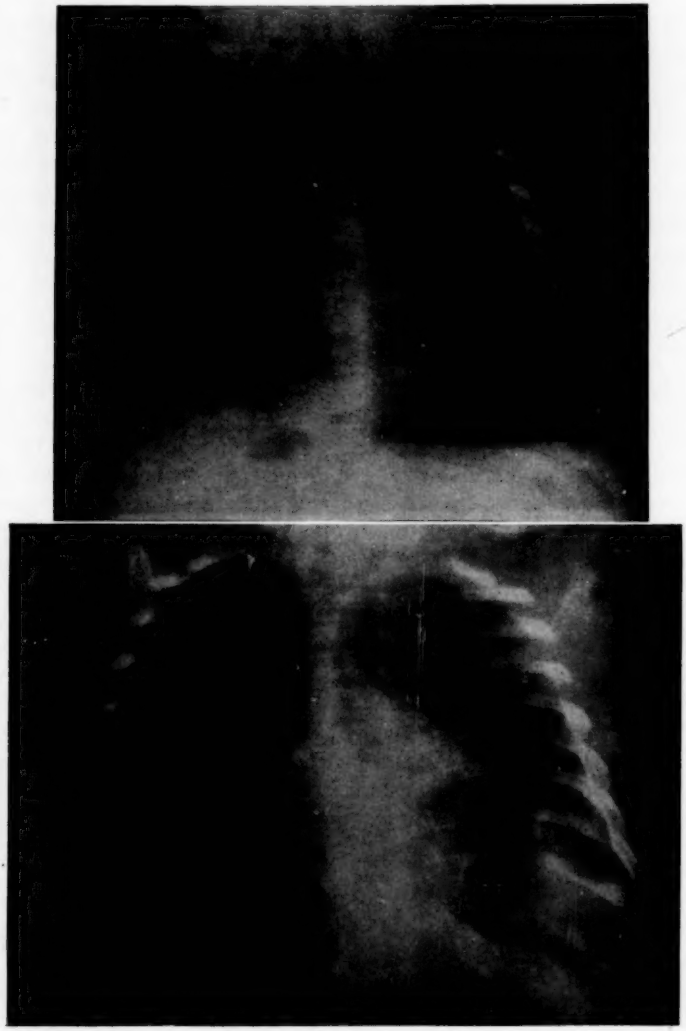
As indicated in Table 35, several infectious agents may cause acute bronchiolitis. It seems, however, that most cases have a viral etiology. Recent studies have incriminated the respiratory syncytial (RS) virus as a relatively common cause.[2]

ANTIMICROBIAL THERAPY. The efficacy of antimicrobials for the treatment of acute bronchiolitis is questionable. The dramatic response observed with therapy of pneumococcal pneumonia has not been observed with most cases of acute bronchiolitis. Nevertheless it seems rational to recommend antimicrobial therapy for the following reasons:

1. A clinical differentiation between acute bronchiolitis and acute bacterial bronchopneumonia of infants is difficult and often impossible. Accordingly, it would be wise to initiate therapy with antimicrobial drugs.

2. Recent studies have indicated that corticosteroid therapy may provide symptomatic relief.[10] Patients receiving this therapy should also be given antibiotics, especially if the causative agent of the bronchiolitis is unknown.

In the absence of a known causative agent it would be wise to provide broad-spectrum coverage. Aqueous procaine penicillin, 600,000



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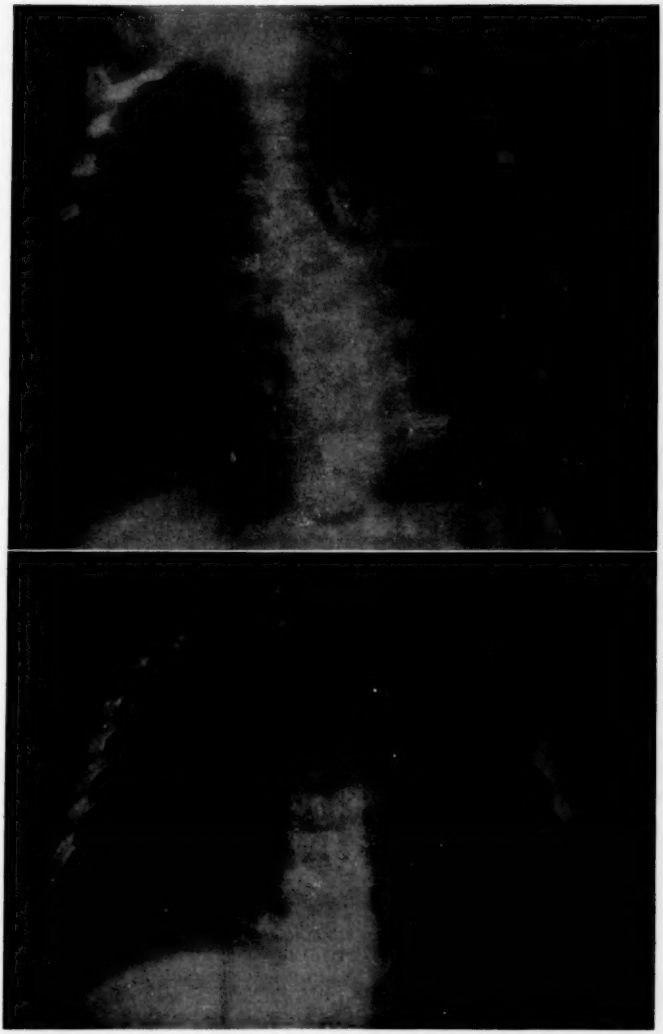

Fig. 24. Roentgenograms of E. R., a 3-month-old infant with acute staphylococcal pneumonia, showing typical progression from consolidation to pneumatocele formation and pyopneumothorax to final resolution. *A*, Roentgenogram taken on admission, Feb. 6, 1958 (third day of illness), showing an area of consolidation in the left mid-lung field. *B*, Roentgenogram taken Feb. 10, 1958 (seventh day of illness), showing pneumatocele formation and pyopneumothorax. The heart and mediastinum are displaced to the opposite side. *C*, Roentgenogram taken Feb. 28, 1958 (twenty-fifth day of illness), showing pneumatoceles, pyopneumothorax and shift of mediastinum still present. *D*, Roentgenogram taken March 28, 1958 (fifty-third day of illness), showing considerable clearing. (From S. Krugman and R. Ward: *Infectious Diseases of Children*. 2nd ed. C. V. Mosby Company.)

units intramuscularly once daily, plus either chloramphenicol or tetracycline is recommended.

Acute Pneumonitis

The diagnosis of pneumonia is suggested by the occurrence of fever, cough, respiratory distress and localized pulmonary signs. The etiology is most commonly bacterial or viral. The various etiologic agents responsible for pneumonia are listed in Table 35.

The roentgenogram and blood cell count may provide an early clue to the type of pneumonia. A polymorphonuclear leukocytosis plus lobar consolidation suggests a pneumococcal etiology. The presence of pneumatoceles, empyema or pyopneumothorax implicates the staphylococcus (Fig. 24). A positive blood culture is a helpful diagnostic aid. In general, however, it is difficult to differentiate bacterial from viral pneumonitis during the early stage of the disease.

ANTIMICROBIAL THERAPY. Early specific antimicrobial therapy of bacterial pneumonia in infants and children will prevent unnecessary complications and improve the prognosis. Consequently, antimicrobial therapy should be started as soon as a diagnosis of pneumonia is suspected. The treatment should be aimed at the most probable bacterial cause.

Pneumococcal Pneumonia. Adequate therapy can be instituted with any one of the following antimicrobial drugs: penicillin, tetracycline, erythromycin, chloramphenicol or sulfonamides. Penicillin is undoubtedly the most effective drug. A dramatic response to therapy is usually observed within one to two days. Treatment should be continued for at least five days after the temperature has become normal. The following dosage schedules are suggested:

PENICILLIN:
- (*a*) aqueous procaine penicillin, 600,000 units intramuscularly once daily, or
- (*b*) penicillin by mouth, 300,000 to 500,000 units 4 times daily, or
- (*c*) a single intramuscular inoculation of aqueous procaine penicillin, 600,000 units, combined with benzathine penicillin G, 600,000 units. This preparation is available in a 2-ml. vial. It is well tolerated,[8] and it provides a blood level bactericidal for pneumococci for at least 10 days after a single injection (Fig. 23).

TETRACYCLINE: 25 mg. per kilogram of body weight daily in 4 doses by mouth

ERYTHROMYCIN: 50 mg. per kilogram of body weight daily in 4 doses by mouth

CHLORAMPHENICOL: same dose as erythromycin

SULFADIAZINE
SULFISOXAZOLE
TRIPLE SULFONAMIDES
} 200 mg. per kilogram of body weight daily in 4 doses

Many cases of pneumococcal pneumonia can be treated effectively with a single injection of a mixture of aqueous procaine penicillin, 600,000 units, and benzathine penicillin G, 600,000 units. The dramatic response to this therapy in a nine-year-old boy with pneumococcal tonsillitis and pneumonia is described in the following case report and illustrated in Figure 25.

CASE REPORT. T.A., a 9-year-old boy, was seen on his first day of illness (9/20/1960) after sudden onset of fever, sore throat, anorexia and vomiting. Physical examination revealed fever (104.5° F.), follicular tonsillitis and a polynucleosis (30,000 white blood cells with 93 per cent polymorphonuclear leukocytes). The initial clinical impression was streptococcal tonsillitis. Accordingly, the patient was inoculated with a single intramuscular dose of a 2-ml. mixture containing aqueous procaine

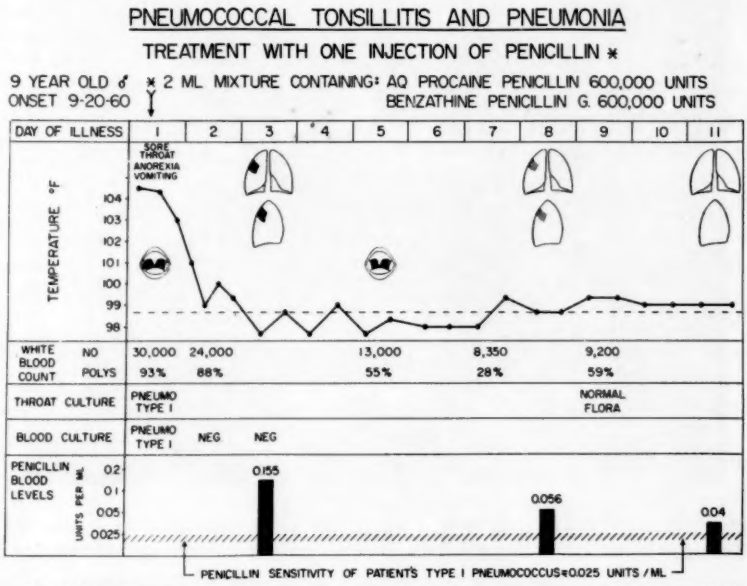

Fig. 25. Treatment of type 1 pneumococcal tonsillitis and pneumonia with a single injection of a penicillin preparation containing 600,000 units of aqueous procaine penicillin and 600,000 units of benzathine penicillin G. Note the dramatic subsidence of fever, the clearing of the exudative tonsillitis and pulmonary consolidation, and the rapid elimination of the type 1 pneumococci from the throat and blood. The penicillin blood level at 11 days (0.04 unit per ml.) still exceeded the sensitivity of the patient's type 1 pneumococcus (<0.025 unit of penicillin per ml.).

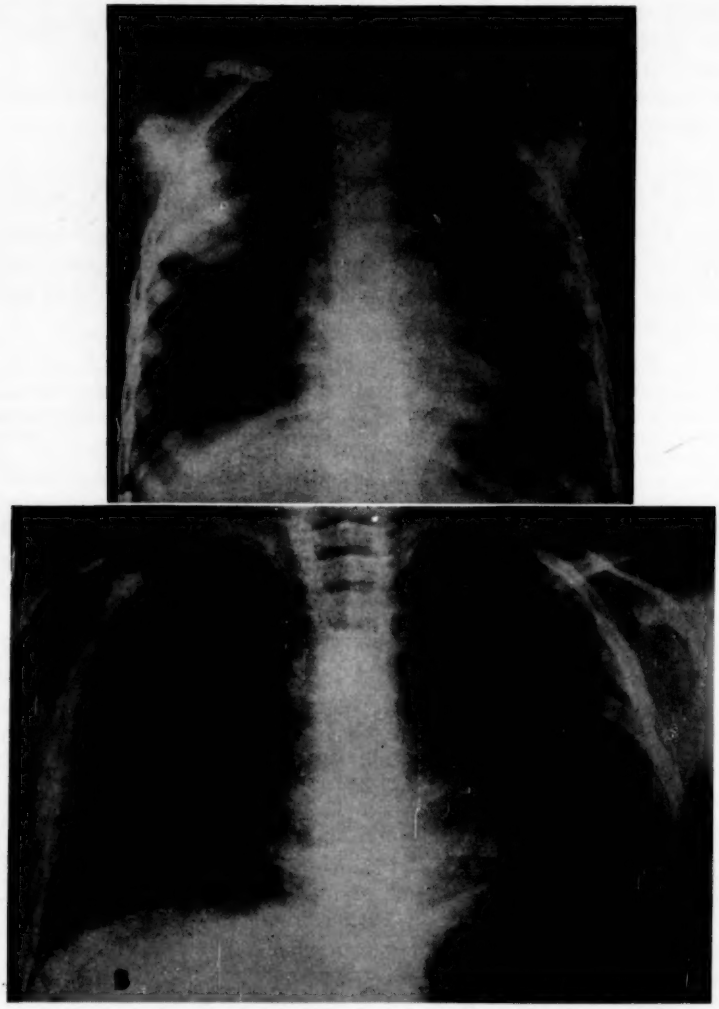

Fig. 26. A, Roentgenogram of chest (patient T.A., Figure 25) taken on third day of illness, showing consolidation of the posterior segment of the right upper lobe. B, Roentgenogram taken on eleventh day of illness, showing clearing of the consolidation.

penicillin, 600,000 units, and benzathine penicillin G, 600,000 units. The following day (9/21/1960) the admission throat culture and blood culture were reported positive for pneumococci, type 1. No additional therapy was given. Blood cultures obtained on September 21 and 22 were negative. A roentgenogram of the chest taken on September 22 (third day of illness) revealed a consolidation of the posterior segment of the right upper lobe (Fig. 26, A).

Fever subsided within 24 hours after initiation of penicillin therapy. The exudate disappeared from the tonsils by the fifth day. In spite of roentgen evidence of pneumonia, no cough was present. Pulmonary consolidation showed considerable clearing by the eighth day and was gone by the eleventh day (9/30/1960), as indicated in Figure 26, *B*.

Blood levels were determined 3, 8 and 11 days after the single injection of penicillin. As indicated in Figure 25, the levels of 0.155, 0.056 and 0.04 unit per milliliter exceeded the penicillin sensitivity of the patient's type 1 pneumococcus.

Staphylococcal Pneumonia. In infants this illness usually begins as an upper respiratory tract infection. The symptoms progress rapidly with increasing cough, tachypnea, dyspnea, subcostal retractions, and fever. Subsequently there may be abdominal distention, pallor, cyanosis, prostration and possibly death. The physical findings vary with the pulmonary involvement, e.g. consolidation, abscess formation, pneumatoceles, empyema, pneumothorax or pyopneumothorax. The typical roentgen findings of rapidly changing infiltration, pneumatoceles, pneumothorax and empyema are illustrated in Figure 24.

Staphylococcal pneumonia in an infant is an acute medical emergency. The chances for survival will be significantly improved by *early*, *optimum* and *intensive* antimicrobial therapy. Delay in therapy may be followed by an irreversible chronic suppurative process.

The various antistaphylococcal drugs recommended for the treatment of severe infections are listed in Table 36. As a general principle it may be wise to use one of the bactericidal drugs (penicillin, bacitracin, vancomycin or kanamycin) plus one of the bacteriostatic drugs (chloramphenicol, erythromycin, novobiocin or ristocetin). Streptomycin and tetracyclines have been less effective in recent years. Sodium dimethoxyphenyl penicillin, a new penicillin which is not inactivated by staphylococcal penicillinase, has minimized the need for combination therapy.[3]

The patient's clinical response and the results of sensitivity tests will influence subsequent changes in therapy. The duration of antimicrobial therapy must be individualized. It may range between two weeks and two months, dependent upon the extent of pulmonary involvement and the presence or absence of complications.

Hemophilus Influenzae Pneumonia. The clinical manifestations are similar to those of pneumococcal pneumonia. Failure to respond to penicillin therapy may provide the first clue to the correct diagnosis, which is confirmed by a positive nasopharyngeal or blood culture. Chloramphenicol or streptomycin therapy is indicated.

Viral Pneumonia. Most viral pneumonias are self-limited infections which are not affected by antimicrobial therapy. Psittacosis, one of the larger viruses, will respond to tetracycline therapy. A recent study has indicated that demethylchlortetracycline is an effective therapeutic

TABLE 36. *Antimicrobial Drugs for Therapy of Severe Staphylococcal Infections**

DRUG	DOSE†			TOXICITY	REMARKS
	Oral	Intramuscular	Intravenous		
Penicillin:					
Aqueous crystalline		8–12 million units/day in 4 doses	8–12 million units/day in 6 doses	Rare in children	
Sodium dimethoxyphenyl		100 mg./kg. of body weight/day in 4 doses	100 mg./kg. of body weight		Poor gastrointestinal absorption
Bacitracin	2000 units/kg. of body weight/day in 4 doses	600–1000 units/kg. of body weight/day in 3 doses Maximum: 50,000 units/day		Nephrotoxic	Poor gastrointestinal absorption
Vancomycin (Vancocin)			40–50 mg./kg. of body weight/day in 2 doses Maximum: 2 gm./day	Pain at site of injection Phlebitis	Poor gastrointestinal absorption
Kanamycin (Kantrex)	100 mg./kg. of body weight/day in 4 doses	25–50 mg./kg. of body weight/day in 3 doses Maximum: 2 gm./day		Nephrotoxic Deafness	Poor gastrointestinal absorption
Chloramphenicol (Chloromycetin)	100 mg./kg. of body weight/day in 4 doses Maximum: 2 gm./day	100 mg./kg. of body weight/day in 3 doses Maximum: 2 gm./day	100 mg./kg. of body weight/day in 3 doses Maximum: 2 gm./day	Aplastic anemia (very rare)	Excellent gastrointestinal absorption

Erythromycin (Erythrocin; Ilotycin)	50 mg./kg. of body weight/day in 4 doses Maximum: 2 gm./day		30 mg./kg. of body weight/day in 3 doses Maximum; 1 gm./day	Nausea Vomiting Superinfection (not common)	Good gastrointestinal absorption
Novobiocin (Albamycin; Cathomycin)	25–40 mg./kg. of body weight/day in 4 doses Maximum: 1–2 gm./day	25 mg./kg. of body weight/day in 2 doses Maximum: 1 gm./day	25 mg./kg. of body weight/day in 2 doses Maximum: 1 gm./day	Rash Drug fever Diarrhea Granulopenia	Good gastrointestinal absorption
Ristocetin (Spontin)			25 mg./kg. of body weight/day in 2 or 3 doses Maximum: 2 gm./day	Rash Thrombophlebitis Drug fever Neutropenia	Poor gastrointestinal absorption

* Staphylococcal pneumonia, osteomyelitis, septicemia, endocarditis or meningitis.
† For premature and newborn infants one fourth of the dose is recommended.

agent for the treatment of cold-agglutinin-positive primary atypical pneumonia caused by the Eaton (PAP) virus.[7]

A diagnosis of viral pneumonia is usually made by exclusion. Consequently, antimicrobial therapy would be indicated until a bacterial etiology can be definitely excluded. Tetracycline therapy would be indicated for cold-agglutinin-positive primary atypical pneumonia.

Pneumonia of Unknown Etiology. Antimicrobial therapy should be aimed at the most probable bacterial causes of the infection. In infants the suspects would be pneumococci, *Hemophilus influenzae* and staphylococci. Therefore a possible initial choice of drugs would be a combination of penicillin plus chloramphenicol or streptomycin. In older children the most common bacterial causes would be pneumococci, streptococci or cold-agglutinin-positive primary atypical pneumonia. Therefore it may be wise to initiate therapy with penicillin. In the absence of a clinical response, tetracycline may be added.

Otitis Media

A discussion of antimicrobial therapy for diseases of the respiratory tract would be incomplete without a brief consideration of otitis media. Acute purulent otitis media requires early, optimum therapy. In infants most cases are due to pneumococci and *Hemophilus influenzae.* In older children pneumococci and hemolytic streptococci are the most common causes. Consequently a useful and effective combination includes penicillin and a sulfonamide. If the clinical response is not satisfactory, the sulfonamide may be replaced with chloramphenicol or tetracycline.

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ANTIMICROBIAL TREATMENT OF TUBERCULOSIS IN CHILDHOOD

EDWIN L. KENDIG, JR., M.D.

In 1944 Brailey[11] published statistics revealing tuberculosis in childhood to be an extremely serious disease. Among those in her study in whom the prognosis was worst were Negro children under the age of three years who showed a parenchymal lesion on the first chest x-ray after the demonstration of tuberculous infection. This group showed a mortality of almost 36 per cent over a 10-year period, 22 per cent during the first year.

Only two years later Dunphy, Cooke et al.[16] reported the first survivor of tuberculous meningitis, a one-year-old infant treated with streptomycin. The child survived, but was mentally retarded. In 1948 Lincoln[42] noted the cure of 3 cases of miliary tuberculosis treated with Promizole (4,2′ diaminophenyl 5′-thiazolyl-sulfone), and later in the same year she and her associates[41] issued a report on the combined therapeutic approach, streptomycin and Promizole, with the first really encouraging results in the therapy of tuberculous meningitis.

Although streptomycin was the first effective drug in the treatment of tuberculosis in childhood, it had distinct limitations: administration could be accomplished only by the parenteral route; it produced toxic effects involving the eighth cranial nerve, with resultant deafness or vestibular dysfunction, or both; finally, it seemed to have no effect on primary tuberculosis, exerting no deterrent action on the development of such progressions as tuberculous meningitis.

In 1952 isoniazid appeared on the scene, and in 1957 a cooperative study under the direction of the United States Public Health Service[20] indicated that use of isoniazid in the treatment of primary tuberculosis produced a reduction in complications of the disease. The over-all effect of these two therapeutic agents, isoniazid and streptomycin, has been a drastic reduction in mortality from tuberculosis effected during the past 15 years.

Although this review is primarily concerned with the antimicrobial therapy of tuberculosis in childhood, it would seem worth while to point out the value of early diagnosis, an absolute essential for the promotion of an optimal therapeutic result.

A few years ago, in the Child Chest Clinic at the Medical College of Virginia, review was made of 200 children[29] who had tuberculous infection which ranged all the way from a positive tuberculin reaction, with no demonstrable lesion either on physical examination or roentgenogram, to widespread tuberculous disease. None of these children had any symptoms or signs suggestive of any disease process and certainly not of tuberculosis.

Since little reliance can be placed on symptoms, it is apparent that a routine tuberculin test is necessary in order to establish an early diagnosis of tuberculosis in childhood. An intradermal test, using either Old Tuberculin Solution (0.1 mg.) or PPD (0.0001 mg.) should be performed between 6 and 8 months of age and annually thereafter. Although there are problems associated with the tuberculin test, notably the false-positive reactions produced by infection with one of the so-called unclassified mycobacteria, the test is still reasonably specific.[32]

Once diagnosis has been established, proper antimicrobial therapy, as outlined in the ensuing pages, can be promptly instituted.

ANTIMICROBIAL AGENTS

Isoniazid

There is little doubt that isoniazid is the most potent antituberculous agent so far uncovered. When the drug is administered orally, plasma concentration 20 to 80 times the inhibiting concentration of the drug (0.05 microgram per milliliter) may be attained within a few hours,[43] and high concentrations persist for 6 to 8 hours. Isoniazid penetrates freely into the cerebrospinal fluid[18] and into caseous tissue.[5] It is excreted mainly in the urine. Side effects of the drug, which have been described mainly in adults, consist largely in neurotoxic manifestations,[7] probably due to competition for pyridoxine.[8, 9] In children, however, pyridoxine deficiency does not appear to be a problem,[47] although precautions must be exercised during adolescence. Other side effects include gastrointestinal dysfunction and allergic reactions, none of which are usually of serious significance.

Dosage of isoniazid is not yet completely established. There is evidence that in the low dosage of 5 mg. per kilogram of body weight isoniazid is effective in preventing most of the more serious forms of the disease; in the same dosage it has also unquestionably produced a cure in miliary tuberculosis and tuberculous meningitis. But Lanier

et al.[37] have presented evidence that the metabolism of isoniazid varies in different patients. Although claim is made that some patients are rapid inactivators of isoniazid, owing to acetylation of the drug, and it is suggested that isoniazid dosage should be determined in each patient by microbiologic assay before initiation of isoniazid therapy, the exact clinical implication of this finding is not clear.

The question of adequate dosage may be approached in one of two ways. First, since children tolerate isoniazid much better than do adults, the dosage of isoniazid may be increased to 20 or even 30 mg. per kilogram of body weight per day, with maximum daily dosage of 500 mg. Second, it has been demonstrated that para-aminosalicylic acid apparently competes with isoniazid for conjugation in the liver, thereby producing a higher blood level of isoniazid.[28, 46] The present trend in the treatment of tuberculosis, then, is toward the simultaneous use of isoniazid and para-aminosalicylic acid or another antimicrobial agent (streptomycin). Although triple drug therapy has not been shown to have statistical advantage over treatment by two drugs, it is nevertheless preferred by many investigators in the treatment of such serious forms as tuberculous meningitis and miliary tuberculosis.

Isoniazid is available for oral administration in tablets of 50 mg. and 100 mg. or in a flavored syrup containing 10 mg. per milliliter. A preparation for parenteral administration (intramuscular or intrathecal) is also available.

Streptomycin

The isolation of streptomycin from *Streptomyces griseus* in 1944 produced the first effective antimicrobial agent against tuberculosis.

Streptomycin inhibits growth of the tubercle bacillus in concentrations of 1.6 micrograms per milliliter. After parenteral administration the drug rapidly appears in the blood stream, reaching a peak value in two hours,[23] and diffuses into the pleural fluid; it diffuses readily into the cerebrospinal fluid only if there is inflammation of the meninges. In the absence of inflammation of the meninges it does not pass the cerebrospinal fluid barrier to any appreciable extent. The drug is largely excreted in the urine, 80 per cent appearing there within 24 hours after administration.[40] (See also page 1013.)

The principal toxic effect of streptomycin is involvement of the eighth cranial nerve. Although loss of vestibular function may be permanent, children usually adjust to this defect without symptoms. Involvement of the auditory branch constitutes a real danger, however, albeit a much less frequent one now than in the days of prolonged streptomycin dosage. Allergic manifestations, such as fever and dermatitis, may occur, and agranulocytosis has been reported.[19]

Dosage of streptomycin, by intramuscular injection, is 40 to 80 mg. per kilogram of body weight per day, with maximal daily dose of 1 gm. The dosage for small children should be at the lower level (40 mg.), except in meningitis or other fulminating forms of tuberculosis. A single daily injection of the drug should be given during the acute phase of the disease, and this may later be reduced to twice weekly. For a small or emaciated patient the daily dose may be divided into two injections.

Because of the rapid development of drug resistance, streptomycin is never used as the sole therapeutic agent, but is routinely given with at least one other tuberculostatic agent.

Intrathecal administration is still utilized by some investigators, although experience at the Medical College of Virginia has not proved its value and use of the drug in this manner has been discontinued.

Streptomycin is supplied in crystalline form, usually as a sulfate, in vials containing 1 gm.

Para-Aminosalicylic Acid (PAS)

Para-aminosalicyclic acid has some bacteriostatic activity against the tubercle bacillus, and acts to delay the emergence of drug resistance to streptomycin. It was, therefore, of great value when streptomycin was the most effective antimicrobial agent. It also delays bacterial resistance to isoniazid, but such resistance has not been of serious clinical significance in children.

The chief value of PAS lies in the fact that it apparently competes with isoniazid for conjugation in the liver, thereby increasing the amount of free isoniazid in the blood.[28, 46]

PAS is administered orally, is readily absorbed and diffuses to some extent into serous surfaces and reaches the cerebrospinal fluid in small amounts. PAS has no intracellular activity. It is rapidly excreted in the urine.

Toxic effects from the drug are mainly gastrointestinal, but hypokalemia, goitrogenic effect,[12] severe allergic reactions,[55] and jaundice[6] may occur.

In general, children have a much better tolerance for all forms of PAS than do adults, but many are unable to tolerate the high dosage often recommended. The drug should be prescribed in dosage of 200 mg. per kilogram of body weight per day. When the salts of para-aminosalicylic acid (sodium, potassium, calcium) are used, the dose should be correspondingly larger, 250 to 300 mg. per kilogram.

PAS is supplied as a powder, in 0.5-gm. tablets, or as a solution of the sodium salt. Note that the solution is stable for only 24 hours and then only if kept in the dark and refrigerated.

Other Antimicrobial Agents

Pyrazinamide has been found to be an effective drug for a short time,[54] but its ensuing ineffectiveness cannot be correlated with the emergence of pyrazinamide-resistant tubercle bacilli. There has also been much evidence of hepatic toxicity.[44, 50] The Committee on Therapy of the American Trudeau Society[14] concluded that, when used alone, pyrazinamide had only a limited effect, and that its serious hepatotoxic action tended to outweigh its therapeutic value.

Viomycin, another antibiotic derived from a fungus of the streptomyces group, has tuberculostatic properties which make it an available drug in the treatment of tuberculosis.[58] It is, however, less potent than streptomycin and is not devoid of toxicity; it is used only when other treatment is not satisfactory.

Cycloserine is also derived from a member of the streptomyces group. It is not as effective as streptomycin or isoniazid[51] and has shown a number of toxic effects, the tendency toward convulsions being the most important.[56]

Corticosteroids

Apparently cortisone acts to suppress the usual inflammatory response of the body with impairment of granulation tissue formation, macrophage activity and fibroblastic repair.[27] From the nature of this mechanism it appears likely that cortisone promotes progression of tuberculous disease in the lung. This deleterious effect of cortisone can be overcome, however, by specific, effective antimicrobial treatment.[36]

Corticosteroids should be used for the infant or young child who is dangerously ill in order to support him until antimicrobial drugs have an opportunity to produce some effect.[15] Indications for the use of corticosteroids in tuberculous pleurisy with effusion, miliary tuberculosis, tuberculous meningitis, tuberculosis of the superficial lymph nodes, and the endothoracic primary complex will be discussed later.

GENERAL TREATMENT

Removal of the tuberculous contact must be accomplished by means of chest x-ray of all adult contacts, including, of course, grandparents, baby sitters, household servants, and any others who may have been in contact with the child. An evaluation of 80 infants born of mothers who had tuberculosis at time of delivery, shortly beforehand or soon afterward, was recently carried out in Richmond.[31] The most significant finding was the fact that removal of the infant or child from the tuberculous mother was not always enough to prevent later infection in the child. Even though 41 of the children were isolated from

their respective mothers until the mother was sputum-negative, 20, or almost 50 per cent, became infected with tuberculosis when returned to the home environment, 12 of these during the first 2 years of life. It is advised that this particular group receive BCG vaccine.

An adequate diet (high protein) and the usual vitamin supplement for a growing child are indicated, but the question of bed rest varies with the type of disease. Children with asymptomatic primary tuberculosis need no limitation of activity, and even those acutely ill should be allowed some activity as soon as possible, since it has been demonstrated that complete bed rest may result in undesirable negative calcium and nitrogen balance.[26]

Chest x-ray at appropriate intervals is necessary.

Asymptomatic Primary Tuberculosis

Asymptomatic primary tuberculosis may appear in one of three forms: (*a*) positive tuberculin reaction with no other evidence of tuberculous disease on physical examination or by roentgenogram; (*b*) positive tuberculin reaction with roentgenographic evidence of enlarged mediastinal lymph nodes; (*c*) positive tuberculin reaction with x-ray evidence of enlarged mediastinal lymph nodes and a primary parenchymal focus. The most common is a positive tuberculin reaction with no other evidence of disease.

As far as is known, no available antimicrobial agent will eradicate tubercle bacilli. Patients with tuberculosis usually remain tuberculin-positive, even though the disease process appears to be controlled. Conversion from positive to negative tuberculin reaction is not frequent, although there have been reports to the contrary.[1, 2, 3, 10, 45, 52] We have seen twins with negative roentgenograms who reverted from positive to negative tuberculin reaction after isoniazid therapy. The loss of tuberculin sensitivity must be considered unusual, however.

The aim of antimicrobial therapy, therefore, is not only cure of the existing tuberculous condition, but also prevention of the complications of the disease. So far, sufficient evidence is not available for us to assume that antimicrobial therapy is effective in the treatment of primary tuberculosis itself, and no drug other than isoniazid has shown ability to prevent the more serious forms of the disease, such as tuberculous meningitis, miliary tuberculosis and Pott's disease.

That isoniazid, however, is effective in reducing the incidence of the more severe forms of tuberculous disease has been amply documented by the United States Public Health Service study on isoniazid as prophylaxis against tuberculous meningitis.[20] Recent unpublished data from that study indicate that children in the control group had 15 times as many complications of tuberculosis as those in the group

treated with isoniazid in dosage of 4 to 6 mg. per kilogram of body weight per day.[48]

On the basis of this study and other observations, the Committee of the Section on Diseases of the Chest of the American Academy of Pediatrics[13] now recommends that isoniazid be used in the treatment of children with local or x-ray evidence of active tuberculosis; the committee also recommends that all children under three years of age with a positive tuberculin reaction and those who recently converted from a negative to a positive tuberculin reaction be given the benefit of isoniazid prophylaxis. All others in this group must be individualized. Isoniazid therapy in dosage of 10 to 20 mg. per kilogram of body weight should be carried out for a one-year period.

Progressive Primary Tuberculosis (Pulmonary)

The term "progressive primary" lesion indicates any worsening of asymptomatic primary tuberculous disease. Among the pulmonary manifestations may be tuberculous pneumonia, which exists in one of three forms: (1) tuberculous pneumonia at the site of the primary parenchymal focus; (2) tuberculous pneumonia of hematogenous origin, occurring near the close of the so-called incubation or invasion period; (3) tuberculous pneumonia resulting from rupture of a caseous tuberculous lymph node into a bronchus (with associated endobronchial tuberculosis present, although the latter may exist alone).

Atelectasis is another important pulmonary complication. In primary tuberculosis this may occur in either of two ways. There may be an extrabronchial lesion, with the edematous node or mass of nodes so placed as to impinge on the bronchus, causing occlusion of the lumen and atelectasis of that area of the lung distal to it. Or the lesion may be an endobronchial one; i.e. a caseous node may actually penetrate the wall of the bronchus and fill the lumen with caseous or granulomatous material. The lumen becomes occluded, and that area of the lung distal to it is rendered atelectatic. In either case bronchoscopic examination is indicated. If the lesion is an extrabronchial one, nothing can be accomplished, but in due time the node will decrease in size, the lumen of the bronchus will again became patent, and that area of the lung which has been atelectatic will usually become re-aerated. On the other hand, if the lesion is an endobronchial one, some of the caseous or granulomatous material can be removed and patency of the lumen sometimes re-established. Nevertheless treatment of endobronchial tuberculosis is not satisfactory, and there is considerable feeling now that the use of corticosteroids, in conjunction with antimicrobial therapy, may be of value in such instances.

Antimicrobial treatment consists of isoniazid, 15 to 20 mg. per

kilogram of body weight, with maximum daily dose of 500 mg., and para-aminosalicylic acid, 200 mg. per kilogram of body weight, with maximum daily dose of 12 gm. Isoniazid should be given in at least two divided doses and PAS in four divided doses. If the child does not respond satisfactorily to this treatment, it will be necessary to add streptomycin, 40 mg. per kilogram of body weight per day, with maximum daily dose of 1 gm. Streptomycin is continued for one month after satisfactory clinical response, but isoniazid and PAS therapy should be carried out for at least one year, and sometimes longer.

Chronic pulmonary tuberculosis is treated in the same manner.

Tuberculous Pleurisy with Effusion

Tuberculous pleurisy with effusion in infants and young children apparently constitutes a somewhat different problem from that occurring in older children and in adults. The prognosis depends entirely on the underlying lesion,[24] and the pleurisy with effusion actually has little to do with the severity of the disease process, except that it may cause respiratory embarrassment.

Diagnostic aspiration should always be carried out. Isoniazid and PAS are given for a 12-month period. Prednisone, 1 mg. per kilogram of body weight per day, in 4 divided doses, appears to be helpful; it is continued only until pleurisy with effusion appears to be controlled.

Miliary Tuberculosis

Miliary tuberculosis is, of course, a generalized involvement, but the manifestations are more often pulmonary. This is an extremely serious form of the disease, and therapy consists of a triple drug regimen with isoniazid, para-aminosalicylic acid and streptomycin. Isoniazid and para-aminosalicylic acid are continued for at least one year, but streptomycin is given for one month after satisfactory clinical response (for drug dosage see Table 37). Prednisone is indicated for extreme dyspnea, and is used for the period necessary to control dyspnea.

TABLE 37. *Treatment of Miliary Tuberculosis*

DRUG	DAILY DOSAGE	MAXIMUM DAILY DOSAGE	DURATION OF THERAPY
Isoniazid	20 mg./kg.	500 mg.	12 months or longer
Para-aminosalicylic acid	200 mg./kg.	12 gm.	12 months or longer
Streptomycin	40–80 mg./kg.	1 gm.	1 month after satisfactory clinical response
Prednisone	1 mg./kg.	60 mg.	Used only during period of extreme dyspnea

Tuberculosis of the Superficial Lymph Nodes

As a rule, extrapulmonary complications are more serious than pulmonary complications. Among the less serious of extrapulmonary complications is tuberculous involvement of the superficial lymph nodes. This does not occur as frequently as in the days before routine tuberculin testing of cows and the pasteurization of milk, but is still important. Involvement of the superficial lymph nodes occurs at the time of the transient bacillemia when tubercle bacilli are deposited in foci, where they usually remain quiescent until some trigger mechanism may activate them. Since such a trigger mechanism is usually required for activation, this disease process more often occurs in the superficial cervical lymph nodes. Here, quiescent tubercle bacilli are activated by acute tonsillitis or adenoiditis. The bacterial infection is controlled by appropriate antibiotics, but the activated tuberculous process continues.

In any instance, when there is a positive tuberculin reaction and a lymph node which measures 2 cm. or more in diameter and is increasing in size, or there is a node which shows early signs of suppuration, treatment by excision and, of course, isoniazid and PAS therapy for a full year is indicated. If the mass of nodes is too great, or if complete liquefaction of the node has already occurred and excision cannot be carried out, it has been suggested that aspiration of the node (when liquefied) and the use of isoniazid and PAS, plus corticosteroid therapy, may be effective. Prednisone dosage is 1 mg. per kilogram of body weight per day, and is continued until healing is effected. Tonsillectomy is advised only if there are indications for it.

Tuberculous Meningitis

Tuberculous meningitis is the most serious form of tuberculous disease. Before the advent of streptomycin it was presumably 100 per cent fatal. At present with the use of isoniazid, PAS and streptomycin, approximately 75 per cent of such patients admitted to the Medical College of Virginia Hospitals are salvaged. The treatment must consist of a triple drug regimen: isoniazid in dosage of 20 mg. per kilogram of body weight per day (maximum 500 mg.); PAS in dosage of 200 mg. per kilogram of body weight per day (maximum 12 gm.); and streptomycin in dosage of 40 to 80 mg. per kilogram of body weight per day (maximum 1 gm.). The first two drugs are given for at least one year,[33, 35] and streptomycin is given for one month after satisfactory clinical response. Indeed, after about one month of daily streptomycin therapy, administration of this drug is often reduced to twice weekly, then finally discontinued. Antimicrobial agents appear to be reasonably effective in the treatment of tuberculous meningitis *if* they can reach the organism. Use of prednisone may decrease the likelihood of cere-

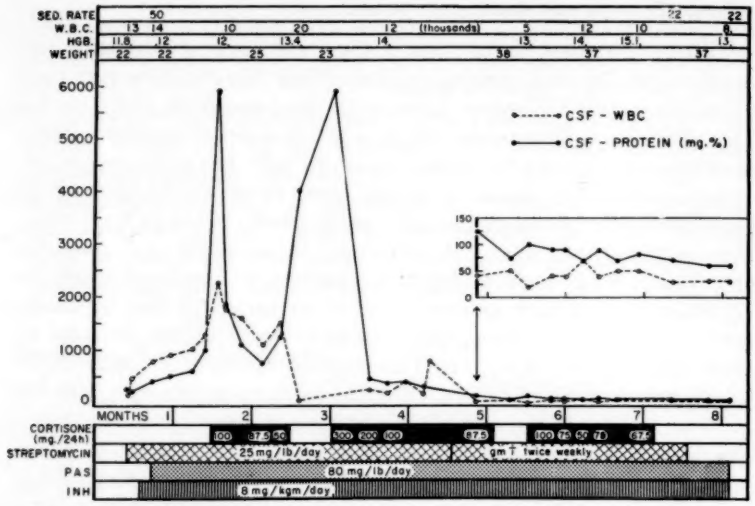

Fig. 27. Diagram depicting precipitous fall of cerebrospinal fluid protein when cortisone therapy was instituted. (Courtesy of *Am. Rev. of Tuberculosis and Pulmonary Diseases.*)

brospinal fluid block, and in addition, reduction of the inflammatory process may lessen the danger of irreversible thrombotic phenomena.

The efficacy of cortisone in the control of cerebrospinal fluid block is exemplified in Figure 27.

During the period before the effectiveness of corticosteroid therapy in prevention and dissolution of cerebrospinal fluid block had become recognized, a two-year-old Negro girl had such a block. Cerebrospinal fluid protein was 5600 mg. per 100 ml. when therapy with cortisone was instituted. After 2 weeks cerebrospinal fluid protein was 650 mg. per 100 ml., but as dosage of the drug was decreased and finally discontinued, the cerebrospinal fluid protein gradually rose to 5800 mg. per 100 ml. When it then became apparent that the block could be controlled by cortisone, such therapy was again instituted and the block rapidly dissolved.

Tuberculosis of the Bones and Joints

As recommended by the Committee on Tuberculosis and Respiratory Diseases in Childhood of the American Trudeau Society,[15] tuberculosis of the bone and joints is treated with isoniazid and PAS for 18 to 24 months. All superficial and accessible abscesses should be drained. Immobilization is not necessary in the nonweight-bearing structures; if, however, weight-bearing structures are involved, whatever means are necessary to prevent weight-bearing are carried out.

Renal Tuberculosis

For renal tuberculosis, triple drug therapy, using isoniazid, PAS and streptomycin, is indicated.[38] This treatment should be carried out for

2 years, but the dosage of streptomycin (20 mg. per kilogram) is not as large as that suggested earlier. Treatment for renal tuberculosis should be carried out if *Mycobacterium tuberculosis* is isolated from urine culture even though the pyelogram is negative, and it is always indicated when *Mycobacterium tuberculosis* is isolated on culture and there is also an abnormal pyelogram.

OTHER INDICATIONS FOR ANTIMICROBIAL THERAPY

Any tuberculin-positive child who receives corticosteroid therapy for another disease should be given concurrent isoniazid therapy.

Since it is generally recognized that measles causes deterioration of tuberculous disease,[39, 59] and it has been demonstrated that isoniazid is effective in preventing this deterioration,[34] isoniazid therapy should be given for a minimum of four weeks in any tuberculin-positive child who contracts measles. The same therapy should be utilized in the tuberculin-positive child with pertussis.

PREVENTION OF TUBERCULOSIS

To date, only two methods have been demonstrated to be reasonably effective in preventing tuberculous infection: isolation of those adults with infectious tuberculosis, and the use of BCG vaccine. BCG vaccination has been conclusively shown to increase resistance against exogenous tuberculous infection,[4, 17, 25, 53, 57] and it is mainly of use in those children living in a home in which there is an adult with infectious tuberculous disease, or one with potentially infectious tuberculous disease, such as a mother who has been discharged from a sanitorium with apparently arrested tuberculosis. It is also useful in those population groups in which there is a high incidence of tuberculous infection, such as that economic group attending the Well Baby Clinic at the Medical College of Virginia.[30]

Ferebee and Palmer[21] and Palmer, Ferebee and Hopwood[49] have reported results of studies on guinea pigs suggesting the possibility that isoniazid may be used to prevent tuberculous infection. The United States Public Health Service[22] is now carrying out a controlled study on the use of isoniazid in household contacts of tuberculous persons. Results of this study should prove or disprove the efficacy of isoniazid in the prevention of tuberculosis.

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ANTIMICROBIAL THERAPY IN HEART DISEASE IN CHILDREN

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The prophylactic and therapeutic use of antimicrobial agents has altered the incidence and clinical picture of heart disease. Bacterial endocarditis, almost invariably fatal before the antibiotic era, can be prevented or treated. In its prevention in susceptible persons, the necessity of antibiotics, the choice of appropriate drugs and the method of administration have all been questioned. Endocarditis treatment rapidly changes as diseases are created by antibiotic therapy,[46] as bacteria develop resistance to known agents, and as newer antibiotics[78] are developed. In this report current problems and concepts of chemoprophylaxis and therapy of bacterial endocarditis will be discussed.

Appropriate therapy of streptococcal infections has decreased the incidence of initial and recurrent attacks of rheumatic fever. Controlled evaluation demonstrates that appropriate antibiotic therapy reduces the incidence of overt rheumatic fever following streptococcal infection. It is not yet known whether carditis and rheumatic heart disease are also prevented. In this discussion, present recommendations for combating the streptococcus will be outlined and evaluated.

In spite of the obvious benefits of antibiotic therapy, reports[46] have appeared of diseases and death seen only since the advent of antibiotics, and some believe that improper use of antibiotics may even increase the incidence of bacterial disease. That "general bacterial infections are causing more deaths now"[22] than before the use of sulfonamides or antibiotics is a frightening thought. This report will deal with some aspects of the improper uses of antibiotics and their implication in the production of disease.

PROPHYLAXIS OF BACTERIAL ENDOCARDITIS IN SUSCEPTIBLE PERSONS

General Chemoprophylaxis

The concept of prevention of disease by routine immunization and dietary measures has now been extended to include prevention by prophylactic antibiotic therapy. Chemoprophylaxis has proved invaluable in many instances in which a single agent was used against a single pathogen.[75] Specific examples are the use of penicillin in preventing gonococcal or streptococcal infections and the use of sulfonamides in preventing spread of the meningococcus.[102] In contrast, the nonspecific use of broad "covering" antibiotics not only has failed in its purpose, but also has led to toxic and allergic reactions, to superinfection with resistant species, to unnecessary expense and to masking of complicating infections.[75] Well controlled studies have demonstrated the inadequacy and hazards of prophylactic antibiotic therapy in measles,[103] poliomyelitis,[49] heart failure,[72] coma,[73] with steroid therapy[32] or with the use of indwelling urologic catheters.[73] The mounting evidence against the general prophylactic use of antimicrobial agents has led Hodes[37] to suggest that such therapy should be limited to "certain specific indications." Since the prevention of bacterial endocarditis is essentially the prevention of bacteremia, he feels that children with rheumatic or congenital heart disease should be protected against transient bacteremia. Risk of bacterial endocarditis is particularly high after dental extraction, and gastrointestinal or urologic operations.

Confusion has resulted from failure to recognize that the performance of certain procedures on patients with cardiac lesions constitutes one of the specific indications for antibiotic prophylaxis. In the susceptible patient antibiotics are administered *not to prevent postoperative infection* per se, but *to decrease the incidence of bacteremia associated with the surgical procedure.*

The Susceptible Person

Feinstein[23] states that the predisposing lesion in bacterial endocarditis is rheumatic in 90 per cent and congenital in 5 per cent, with involvement of normal valves in the remaining 5 per cent. Recent reports[53, 56] indicate that the incidence of infection in congenital heart disease has increased, probably related to increased longevity and more frequent surgical intervention in these patients. With this change there has been a decreased incidence of rheumatic fever and rheumatic heart disease.

Bacteremia may occur after dental manipulation,[25, 31, 36] and after oral,[25, 57] respiratory,[14, 31] cardiac,[53, 56] genitourinary[23, 65] or gastrointestinal surgery.[2] Predisposing conditions include leukemia, lymphomas, diabetes, exfoliative dermatitis or steroid therapy. In general, in

the patient with a normal heart, better results are obtained by withholding antibiotics, by careful attention to the patient, and by early recognition of infection followed by specific therapy in full dosage.[102] On the other hand, in the patient with heart disease, prophylactic agents are necessary because of the risk of bacterial endocarditis.[2]

Specific Indications and Agents

Dental manipulations and oral operations have long been recognized[33, 36, 44] as important causes of bacteremia and bacterial endocarditis in patients with heart disease. Before antibiotics, attempts to remove infective foci in the oral cavity often resulted in death from the very infection that the operation was attempting to prevent. Today there is agreement that prophylactic agents should be used before dental and other oral operations for prevention of bacteremia in susceptible cardiac patients. It is not known, however, just how long before the procedure antibiotics should be given. The risks of inadequate effect of antibiotics administered just before operation must be weighed against the hazards of emergence of antibiotic-resistant organisms with prolonged preoperative treatment.[2]

Dental Surgery. The administration of penicillin or sulfadiazine one hour before tooth extraction is effective in reducing the incidence of bacteremia.[33, 80] The risk of bacteremia is greatest with poor condition and infection of the gums and with more extensive surgery.[36] An optimal prophylactic plan is the use of intramuscular injections of 600,000 units of procaine penicillin for 2 days before operation and continued for 2 days afterwards, supplemented by 600,000 units of crystalline penicillin one hour before operation.[2] A combination of oral and intramuscular penicillin has also been recommended in which 500,000 units of phenoxymethyl penicillin (penicillin V) are given 4 times a day for 5 days, beginning 2 days before operation and supplemented one hour before it by 600,000 units of intramuscular crystalline penicillin.[2] This latter plan may be indicated when parenteral administration is not feasible, but requires the full cooperation of the patient.

In penicillin-allergic children, erythromycin, 50 mg. per kilogram per day (not exceeding 1 gm. per day) given in 4 divided doses, or chlortetracycline,[84] 1 gm. orally one day before extraction, may be used. Local antibiotics in the oral cavity do not reduce the incidence of bacteremia and should not be used.[33]

Tonsillectomy. Rhoads[80] was able to reduce the incidence of postoperative bacteremia from 28.3 to 5.9 per cent by the intramuscular use of 600,000 to 800,000 units of penicillin 4 to 10 days before tonsillectomy. Bacteremia was not reduced by oral or intramuscular peni-

cillin given 12 to 18 hours before operation. Erythromycin and oxytetracycline were likewise ineffective. For this reason a longer period of intramuscular penicillin treatment should be used in the susceptible child undergoing tonsillectomy. Thus 600,000 units of benzathine penicillin administered 7 to 10 days before operation, followed by the regimen outlined under Dental Surgery, has been effective in preventing bacterial endocarditis (unpublished observations).

Other Procedures. A similar regimen combining benzathine and procaine penicillin has been used before cardiac catheterization and bronchoscopy. For genitourinary procedures the incrimination of *Streptococcus fecalis*, enterococci and gram-negative bacteria has led to the use of a combination of penicillin, streptomycin and one of the tetracyclines, all in full dosage for five days, beginning two days before operation.[23]

Cardiac Surgery. Possibly the higher incidence of infection with staphylococci and other bacterial strains following operation[1, 6, 53, 64] is related to excessive antibiotic usage. The use of chloramphenicol and erythromycin has not been successful and has led to the emergence of resistant staphylococci.[23] At the U.C.L.A. Medical Center we administer procaine penicillin intramuscularly for three days before heart surgery, add streptomycin on the day of operation, and continue these drugs together for four or five days after operation.[53] Penicillin alone is continued for an additional three to five days, depending on the general postoperative course. Although this program may cause an increased incidence of infection with the more resistant organisms, failure to utilize prophylaxis might result in a return to the high incidence of subacute streptococcal endocarditis seen in the preantibiotic era.[55, 95] Certainly the recently traumatized intracardiac nidus, lowered patient resistance and possibilities of bacteremia make bacterial endocarditis a great risk at this time. The effect on incidence of endocarditis and involved flora when no prophylactic antibiotics are used in open-heart procedures is now being studied.[45]

TREATMENT OF BACTERIAL ENDOCARDITIS

The widespread use of antibiotics and the remarkable advances in cardiovascular surgery have had a paradoxical effect on bacterial endocarditis. Previously[42] *Streptococcus viridans* was the offending organism in 85 to 95 per cent of cases. With the advent of antibiotic therapy the incidence of bacterial endocarditis decreased, but other, more resistant organisms, particularly the staphylococcus, assumed increasing significance.[64] With the advent of open-heart surgery the clinical and bacteriologic pictures underwent further changes.[53]

Cure is now possible in 90 per cent of endocarditis due to a suscep-

tible organism.[26] The present over-all cure rate of 70 per cent is the same as when penicillin was the only available antibiotic.[31] The continued high mortality rate in spite of the rapidly increasing antibiotic armamentarium is probably related to the emergence of resistant strains and the increased number of infections due to unusual organisms.

Table 38 summarizes antibacterial agents and dosages recommended for the more common coccal endocarditides. Dosages are based on adult weight and, except for penicillin, should be decreased proportionally for children. Table 39 summarizes the treatment of bacterial endocarditis due to less common etiologic agents. Table 40 is a list of the antibiotics in common use, pediatric dosage per kilogram, maximum daily dose, and complications.

The recommended dosage may be toxic for a given patient.[67] On the other hand, in endocarditis due to a resistant organism, it may be lifesaving to use a toxic drug for an extended period.[39] In prematures, in early infancy,[105] and with renal insufficiency, lower dosage must often be given. With awareness of their limitations, then, these tables may be useful guides in the initiation of therapy.

Isolation of the Organism

Now that specific antimicrobial agents are available, a cure in bacterial endocarditis depends on proper antibiotic therapy, which in turn depends on isolation of the offending organism.[34] A minimum of six cultures should be obtained before therapy is begun. Positive blood cultures are obtainable in 70 to 80 per cent of cases of bacterial endocarditis. There is no correlation between the height of temperature and frequency of positive blood cultures. Most series have likewise failed to demonstrate any advantage of arterial blood cultures, but bone marrow cultures may be of value in the patient who has received antibiotics. In selected cases it may be necessary to stop antimicrobial agents for a few days in order to obtain a positive blood culture.

Selection of Chemotherapeutic Agents

Selection of the proper therapeutic agents is based on identification of the organism, knowledge of the actions and limitations of available drugs, and tests of the interactions of the antibiotic and the infecting bacteria.[67] The usual "disk" tests for bacterial sensitivity are meaningless and misleading in endocarditis, since they measure bacteriostatic rather than bactericidal effects.[39] Plate dilution tests are recommended[31] in initial antibiotic selection, while laboratory evidence of adequacy and efficiency of antibiotic dosage is best evaluated by testing the bac-

(*text continued on p. 1239*)

TABLE 38. *Treatment of Bacterial Endocarditis: Usual Etiologic Agents*

ORGANISM	DRUGS	DOSE (ADULT WEIGHT)	ROUTE	FREQ.	DURATION OF RX	REMARKS
Streptococcus viridans	Aqueous crystalline penicillin G and Streptomycin	600,000 Units	IM	q6h.	2 weeks	
(sensitive to 0.1 unit/cc. or less of penicillin)	"	1 gm	IM	q12h.	1st week	Limit is 1 gm./M.²/day
	"	1 gm.	IM	Daily	2nd week	
(sensitive to 0.2 unit/cc. or more of penicillin)	Penicillin	1 Million U.	IM	q2–3h.	2–3 wks.	Higher dose, greater frequency if organism requires more than 1 unit/cc. of penicillin for inhibition of growth in vitro
	and	1 Million U.	IM	q6h.	Next 3–4 wks.	
	Streptomycin	1 gm.	IM	q12h.	2–3 wks.	
	and	1 gm.	IM	Daily	Next 3–4 wks.	
	Probenecid	500 mg.	PO	q6h.		
Enterococci	Penicillin	1 Million U. or	IM	q2–3h.	6 weeks	Can use erythromycin and streptomycin or erythromycin and bacitracin. CAUTION: do not use dimethoxyphenyl penicillin (Staphcillin)
		20 Million U. (up to 100 Million U.)	IM	Daily (continuous drip)	6 weeks	
	and					
	Streptomycin	1 gm.	IM	q12h.	1st 3 wks.	
	"	1 gm.	IM	Daily	2nd 3 wks.	
	Probenecid	500 mg.	PO	q6h.		
Micrococci						
M. pyogenes var. aureus	Penicillin	1 Million U.	IM	q2–3h.	6 weeks	More frequent after heart operations, also from peripheral infections
M. pyogenes var. albus	Probenecid	500 mg.	PO	q6h.		
(sensitive to 1 unit/cc.)	May add:					
	Vancomycin or	0.5 gm.	IV	q6h.		Use if hospital infection
	kanamycin		IM	q6h.		Not over 20 gm. (deafness)

Resistant to 1 unit/cc.	Erythromycin and either (bacitracin or streptomycin or Chloromycetin or tetracycline) or Novobiocin and either (bacitracin or streptomycin or tetracycline) or Chloramphenicol and either (bacitracin or streptomycin)	Appropriate dosage for weight			Finland states that if above doses of penicillin are not effective in micrococci endocarditis, higher doses will not usually be of help
	Dimethoxyphenyl penicillin (Staphcillin, Bristol)	2 gm.	IM or IV q6h.	1–2 wks.	Initial studies show excellent response in treating "resistant" staphylococci
	"	1 gm.	IM or IV q6h.	3–4 wks.	

Adapted from Finland[26, 28] and others.[31, 67, 74, 78]
IM—intramuscular.
IV—intravenous.
PO—orally.
q2h.—every 2 hours.

TABLE 39. *Treatment of Bacterial Endocarditis; Less Common Etiologic Agents*

ORGANISM	DRUG	REMARKS
Neisseria gonorrhoeae	Penicillin	Rare today
Neisseria meningitidis	Penicillin and sulfonamides	———
Diplococcus pneumoniae	Penicillin	May be associated with meningitis
Aerobacter aerogenes or Escherichia coli or Pseudomonas aeruginosa or Proteus vulgaris	(Streptomycin or polymyxin B) *and* (Chloramphenicol or tetracycline)	Polymyxin B should be used in Pseudomonas; streptomycin for Proteus vulgaris These organisms seen after genitourinary and intestinal surgery
Brucella	Tetracycline and streptomycin	———
Salmonella	Chloramphenicol	Possible synergism with polymyxin B in cases with poor response
Hemophilus influenzae	(Chloramphenicol or tetracycline) *and* Streptomycin	———

TABLE 40. *Dosages, Routes and Complications of Antibiotics in the Treatment of Bacterial Endocarditis in Children*

ANTIBIOTIC	DAILY DOSE/KG.	MAXIMAL DOSE (ADULT SIZE)	ROUTE	COMPLICATIONS
Penicillin	—	Huge doses possible	IM, IV	Allergic reactions, mycoses
Streptomycin	25–40 mg./kg.	2 gm.	IM	Vestibular damage
Tetracycline	25–50 mg./kg. 25–50 mg./kg.	2 gm. 1 gm.	IM IV	Fatty liver, intestinal symptoms
Chloramphenicol	100 mg./kg. 100 mg./kg. 50 mg./kg.	4 gm. 2 gm. 2 gm.	PO IM IV	Aplastic anemia, "gray death" in small infants
Erythromycin	60 mg./kg. 40 mg./kg.	3 gm. 1.5 gm.	PO IV	Nausea, vomiting, fever, mycoses
Novobiocin	50 mg./kg. 25 mg./kg.	2–3 gm. 1–2 gm.	PO IV	Leukopenia
Bacitracin	1000 U./kg.	100,000 U.	IM	Renal damage, nausea, vomiting
Polymyxin B	2.5 mg./kg.	2.5 mg./kg.	IM	Renal damage, fever
Neomycin	10 mg./kg.		IM	Irreversible deafness, reversible renal damage
Vancomycin	40 mg./kg.	2 gm.	IV	Chills, fever, thrombophlebitis, deafness
Ristocetin	25 mg./kg.	3 gm.	IV	Rash, thrombocytopenia, aplastic or hemolytic anemia
Kanamycin	15 mg./kg.	—	IM	Deafness, renal damage

tericidal action of the patient's serum against the organisms previously isolated from his blood stream.[39] Permanently negative blood cultures and clinical improvement leading to cure remain the best indication of successful treatment. Rare instances have been reported[5, 13] of cures in vivo in spite of insensitivity in vitro.

Administration of Antibiotics

Cure of bacterial endocarditis is dependent upon the use of bactericidal antibiotics such as penicillin, streptomycin, vancomycin, neomycin, kanamycin and bacitracin.[74] The bactericidal effects of penicillin can be increased by increased dosage,[39] by the addition of probenecid to raise the blood level,[26] or by the addition of streptomycin.[39] The

bacteriostatic action of erythromycin should always be supplemented by a bactericidal agent.[1]

Antibiotic combinations may synergistically increase bactericidal effects and delay emergence of resistant strains.[79] Often combined treatment, with full dosage of each agent, must be started before the results of cultures and sensitivities are available. The chance must be taken of hypersensitivity, simultaneous development of resistance to antibiotics, and the more rapid development of resistant community and hospital strains.

Treatment with larger doses of a bactericidal drug to which organisms demonstrate only limited sensitivity will probably prove more successful than utilization of a bacteriostatic drug alone.[5, 93] Antagonism between bactericidal and bacteriostatic drugs has not been reported in the therapy of endocarditis. Steroids[74] or antihistaminics[5] may permit continuation of penicillin therapy in an occasional penicillin-allergic patient.

Duration of Therapy

According to present data, bacterial endocarditis should be treated for a minimum of two weeks, regardless of the organism. This short-term therapy should be reserved for organisms extremely sensitive to penicillin, including *Streptococcus viridans, Neisseria pharyngis,* group A hemolytic streptococci, and gonococci.[26, 54] In spite of the extreme sensitivity of the pneumococcus, therapy should be continued for a longer period because of the possibility of a primary hidden focus of infection.[4] In general, one should err on the side of more prolonged therapy in view of the frequency with which relapses require higher dosage and greatly prolonged duration of therapy, and are associated with a poor prognosis. In general, therapy should be extended if (1) the organism is only slightly sensitive or moderately resistant, (2) if there is persistent bacteremia, (3) if fever and other symptoms persist more than one week, (4) if the dose must be interrupted because of intolerance, and (5) if there is a large focal area of suppuration or continued local infection. Occasionally, sterile emboli causing petechiae will persist for weeks after bacteriologic and clinical cure. This situation should not be confused with continuing infection and requires no additional therapy.[26]

Management of Endocarditis with Negative Blood Cultures

It is often recommended[26] that treatment as outlined for *Streptococcus viridans* or the enterococci, depending on the course, be administered to those patients in whom no organism is isolated. Although this may be true for the typical case of endocarditis, more specific clinical clues

are available. Endocarditis after dental or oral surgery is frequently coccal in origin. After genitourinary or intestinal surgery, suspicion of the coliform group is warranted. Micrococcal endocarditis is seen after cardiac surgery or in patients with skin infections. Micrococcal infections acquired at home are more likely to respond to therapy with large doses of penicillin and streptomycin, while hospital infections call for the addition of vancomycin or kanamycin.[74]

Ancillary Measures

Occasionally, additional measures are necessary. In the selected case, surgical ligation of an infected patent ductus arteriosus,[96, 109] embolectomy, resection of an infected aneurysm or removal of a splenic abscess may be necessary for cure.[26] The use of heparin, originally proposed[50] as a possible aid to diffusion of the antibiotic into vegetations, has been discarded because of lack of evidence of beneficial action, and associated complications of embolization, bleeding and allergic reactions. Initial evaluations have not produced any evidence that the administration of steroids along with antibiotics is of any value.

TREATMENT OF STREPTOCOCCAL INFECTION IN THE GENERAL POPULATION

Prevention of Initial Attacks of Rheumatic Fever

Adequate treatment of streptococcal respiratory disease will prevent the development of rheumatic fever and glomerulonephritis.[70, 77] Without therapy, these complications occur in 3 to 5 per cent of the affected population.[23] If treatment is delayed as long as nine days, it is still possible to prevent rheumatic complications.[16] In spite of this, prevention of initial attacks of rheumatic fever has not been completely successful.

One difficulty is that over half of streptococcal infections occur without symptoms.[15, 66] Also, half of school children in large surveys will harbor beta hemolytic streptococci at some time during the school year and yet show no clinical or laboratory evidence of infection.[21, 41] Most respiratory infections in these children will not be associated with streptococci. Not only is prevention of rheumatic fever by eliminating carriers prohibitively expensive, but also recommended treatment has failed to eliminate the streptococcus in some cases.[86]

Diagnosis of Streptococcal Respiratory Disease

The demonstration of group A beta hemolytic streptococci by throat culture is essential for diagnosis. Methods for streptococcal culturing and identification have been well outlined.[99] With experience, clinical

recognition of streptococcal infection is possible with 70 per cent accuracy.[10] Complaint of a sore throat, presence of exudate superimposed on a beefy red throat, and fever over 101° F. suggest streptococcal infection.[92] Cervical lymphadenitis and a white blood cell count over 12,000 aid in diagnosis. Twenty per cent of respiratory infections not associated with these classic symptoms are caused by streptococci. Abdominal symptoms with pain, nausea and vomiting are often present, while cough, coryza and hoarseness are not prominent symptoms in streptococcal infection in childhood. Differentiation from nonstreptococcal disease is more difficult the younger the child, although here, as in all age groups, repeated evaluation improves diagnostic accuracy. Throat culture is still necessary whether streptococcal infection is believed to be a remote or a likely possibility.

Treatment of Acute Streptococcal Disease

Although Breese[11] showed that a single intramuscular injection of 600,000 units of benzathine penicillin G was 94 per cent effective in the treatment of acute streptococcal disease, other studies[90] report a significant rate of relapse or reinfection with this dose. Therefore a single injection of 900,000 to 1,200,000 units of benzathine penicillin G is recommended for the treatment of streptococcal respiratory disease. Pain at the injection site is the price for this most efficient method of streptococcal eradication. Intramuscular procaine penicillin, 300,000 to 600,000 units every other day for 4 doses, or procaine penicillin with aluminum monostearate in oil, 300,000 to 600,000 units given intramuscularly every third day for 3 doses,[73, 91] offers no particular advantage over the single injection of repository penicillin. In view of occasional treatment failures,[15, 78, 104] eradication of streptococci should be proved by culture in all cases.

Buffered penicillin G or phenoxymethyl penicillin (penicillin V), 200,000 to 250,000 units 3 times a day for 10 days, is also recommended[12] and has been effective in all but a few instances.

In children sensitive to penicillin, oral administration of erythromycin[30, 102] in full dose for 10 days has been reported to be as effective as penicillin in treating acute streptococcal infection. Its bacteriostatic rather than bactericidal effect and the uncertainties of oral administration make it less suitable.

The sulfonamides are not effective in eradicating streptococci and should not be used in treating acute streptococcal infections.[16, 20] Antibiotic troches and lozenges are likewise ineffective and introduce hazards of altered oral flora and sensitization.

PREVENTION OF STREPTOCOCCAL INFECTIONS IN RHEUMATIC PERSONS

The decline in incidence of acute rheumatic fever has undoubtedly been accelerated by the discovery and use of effective antimicrobial agents against the streptococcus. Prevention of the initial attack and recurrences of rheumatic fever is now possible with adequate therapy and prophylaxis. The apparent incidence of rheumatic fever has been reduced by 96 per cent, but only long-term studies will determine whether carditis and chronic valvular damage are likewise prevented.[92] Caution is necessary in view of the delayed appearance of rheumatic heart disease in almost half of the patients in one series[7] who had recovered from initial episodes of rheumatic fever without apparent cardiac damage.

Prophylaxis should be administered to all persons who have a well documented history of rheumatic fever or chorea, or who show evidence of rheumatic heart disease.[2] It has been suggested that children of 2 rheumatic parents should receive prophylaxis from an early age since the incidence of rheumatic fever in these children approaches 100 per cent.[107] Prophylaxis is initiated after eradication of the streptococcus in acute rheumatic fever, and when the patient is first seen in all other cases. Rheumatic fever recurrences decrease during summer months, or as the patient becomes older, or as the interval increases since the last attack.[69] In spite of this, streptococcal exposure and infection can occur throughout the year and throughout life. Prophylaxis should therefore be administered continuously and indefinitely.

Prophylactic Drugs in Rheumatic Patients

In 1939 Coburn[20] showed that the sulfonamides are effective in preventing streptococcal infection and rheumatic sequelae. Failure in treating acute streptococcal disease and the high incidence of toxicity were recognized. These findings are equally true today.

Penicillin is equally effective in prophylaxis and, in addition, has an eradicative effect on the streptococcus. The relatively high cost of penicillin is balanced by its lower incidence of general toxic reactions and lack of necessity of performing laboratory studies to detect hematologic toxicity.[59]

Erythromycin[88] and chlortetracycline[62] have also been used, but there is no need to look further than sulfadiazine for effective prophylaxis in children unable to tolerate penicillin.

All agents used in the low recommended prophylactic dosage have been effective in preventing recurrences, with no great changes in

bacterial flora, with rare complications and with no development of resistant streptococci.[23]

Drugs, Dosages and Routes

The drug of choice for penicillin prophylaxis in rheumatic patients is benzathine penicillin G, administered intramuscularly once a month.[17, 108] A slightly higher incidence of reactions occurred in one series when the maximal dose of 1,200,000 units was given,[18] but since rheumatic fever has occurred when 600,000 units were given, the present recommended dose is 900,000 to 1,200,000 units. This method makes breaks in the prophylactic regimen less likely, allows more careful observation of the patient, achieves a bactericidal level each month and is the cheapest and most highly effective method of streptococcal prophylaxis. Pain is usual at the injection site, but more severe reactions are, in general, no more frequent than with other forms of penicillin.[38] In the first year or two after acute rheumatic fever, when the recurrence rate is higher, a monthly injection of benzathine penicillin G should be given rather than oral medication.

Oral administration of buffered penicillin tablets, 200,000 to 250,000 units twice daily, is a frequently used method of prophylaxis and is probably the next most effective method. The previously recommended lower dosages have been ineffective in preventing streptococcal infections in susceptible persons.[58] Oral benzathine penicillin or alpha-phenoxyethyl penicillin (Syncillin, Bristol) do not produce higher levels or less toxicity.[12]

Other methods of penicillin prophylaxis have been proposed, but their effectiveness has not been proved. Lim and Wilson[52] found no difference in the recurrence rate of rheumatic fever by eliminating prophylaxis and treating streptococcal infections as they appeared. One disadvantage is that the asymptomatic streptococcal infection might not be seen or treated in such a program.

Kohn[47] recommends oral administration of 800,000 units of penicillin for 7 days of each month, with 2 monthly periods of penicillin administration during seasons of known peak streptococcal incidence. He feels that this intermittent bactericidal dose is safer, cheaper and equally effective.

In the patient allergic to penicillin, oral sulfadiazine in a daily dose of 0.5 gm. in children under 60 pounds and 1 gm. in all others is as effective as oral penicillin.[48, 59, 91] Recently, prophylaxis has been successful with sulfamethoxypyridazine (Kynex), in a dose of 2 gm. for children under 100 pounds and 3 gm. for children over 100 pounds, given orally once a week.[40] Toxic reactions, including rashes and agranulocytosis, should be watched for, particularly in the first two months of sulfonamide administration.[20]

In children unable to take penicillin or sulfonamides, erythromycin[88] or tetracycline[62] can be used in a daily oral dose of 250 mg.

SUMMARY

Great changes have occurred in congenital and acquired heart disease since the advent of effective antimicrobial agents. In congenital heart lesions, antibiotics have been useful in the prevention and treatment of bacterial endocarditis. Careful attention to details of proper drugs and dosages is essential to their maximum and continued usefulness.

Initial and recurrent episodes of rheumatic fever can now be controlled. Present therapeutic and prophylactic regimens for combating the streptococcus have been outlined and evaluated.

Awareness of the principles and details of administration of antimicrobial agents is necessary for optimal care of the patient with heart disease. Proper drug usage will enhance their effect in the individual and the community.

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ANTIMICROBIAL THERAPY FOR SURGICAL GASTROINTESTINAL DISEASES

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Surgical diseases of the gastrointestinal tract which have benefited most from the introduction of antimicrobial agents are those for which preoperative preparation of the colon can be carried out and an elective procedure performed. Intestinal antisepsis has gained progressively wider acceptance among surgeons who deal with surgical diseases of the colon in adults. A similar acceptance has not found such ready favor with those whose practice concerns itself more with children, as witness these comments on pediatric surgery. Gross[8] says: ". . . [We] rely mostly upon cleansing irrigations to prepare the bowel. . . . We place little emphasis or reliance upon . . . drugs for reducing the bacterial flora of the intestinal contents." Potts[9] believes that the bowel should be "cleaned and sterilized with neomycin" as part of the preoperative preparation in Hirschsprung's disease. Ariel and Pack[1] recommend sulfathalidine and neomycin in discussing polyps of the colon: "In preparing the colon for surgery, not only is it necessary to have the bowel free of fecal matter, but the bacterial contents must also be reduced to a minimum." The precautionary statements of Swenson[11] should be heeded by all: "While patients who are to undergo surgery on the intestinal tract may benefit from a liquid diet and enema and saline laxatives, the value of chemotherapeutic agents like sulfasuxidine and sulfathalidine is not overwhelming. However, they may be used provided the surgeon does not assume he can take chances on an inadequate anastomosis or intestinal closure because the bowel has been prepared by chemical agents. It is far better to strive for a perfect anastomosis and to worry less about the preparation of the intestinal tract with bactericidal agents."

If antimicrobial therapy can be properly chosen and properly used, we believe that there is a place for it in the surgery of infants and children, just as there is in the treatment of adults. Nevertheless, the different response of children requires selection of different drugs, and appreciation of this difference is essential for an intelligent selection.

If there is disagreement about the value of antibiotics for elective surgery of the colon in children, there is little or none about the use of these agents for surgery in other parts of the gastrointestinal tract. There is almost universal agreement that there is no place for these agents in the elective surgery of other parts of the gastrointestinal tract, except so far as this kind of surgery may be undertaken as an emergency procedure in children who are at the moment particularly susceptible to some other infection not related to their gastrointestinal disease.

Most of the congenital anomalies of the gastrointestinal tract which require surgery are treated as emergency or semi-emergency surgical problems, and thus there is no time for preoperative intestinal antisepsis, regardless of whether or not it might have a value. It is the general policy of this department that there is no need for preoperative intestinal antisepsis in esophageal, gastric, pancreatic, biliary or small intestinal surgery regardless of whether the patient be a child or an adult. We have no objection, however, to prophylactic antibiotics for newborn infants and older children to prevent pulmonary complications.

Thus preoperative antimicrobial therapy for surgical gastrointestinal diseases is actively advocated only for lesions which involve the colon. This thinking dominates our use of the drugs in children just as much as it does in adults. Another dominant feature of our thinking is that the use of antibiotics is only one of many adjuvants to surgical therapy, and is in no way intended to provide a means of permitting surgical procedures that would not otherwise be deemed safe in the same patient under identical conditions.

Strong advocacy of intestinal antisepsis requires experimental proof of the value of these agents. This has been obtained in an experimental study of colonic anastomoses made under the extreme stress of devascularization of one side of the anastomosis.[6] Under these conditions antibiotics protected the anastomosis and permitted survival of the animal. This was in contrast to the rapid disintegration of the devascularized anastomosis in the unprotected controls, which died of massive peritonitis. On the basis of this positive evidence of the value of antibiotics in colon surgery, a policy for routine use of antibiotics in colon surgery was placed in effect on our service in July, 1955.[2, 3]

Since that time bowel preparation has been utilized in over 300 patients, 9 of whom were under the age of 2 years, the youngest being

6 weeks, and 6, 10 and 12 months respectively. Children under the age of 12 have had intestinal antisepsis for Hirschsprung's disease, polyps, colostomy closure, intussusception, imperforate anus, rectourethral fistula, and for colon transplants (Table 41).

Once it had been decided to use routine preoperative intestinal antisepsis for elective colon surgery, it was desirable to know which agent or agents would be suitable for this purpose. A study was undertaken of the effect of numerous antimicrobial agents on the intestinal flora of hospitalized patients.[2, 3] For this purpose adult patients with no known disease of the gastrointestinal tract were placed upon a low residue diet, a cathartic the first day of therapy, and daily enemas. They were given the selected antimicrobial agent for 72 hours (except in the earlier part of the study, when the drugs were administered for 5 days). Stools were analyzed each day before, during and after therapy by

TABLE 41. *Indications for Intestinal Antisepsis in Infants and Children*

MAJOR INDICATIONS
Hirschsprung's disease
Polyps of the colon
Colostomy closure
Colon transplant
Any other lesions in the colon
LESS COMMON INDICATIONS
Melena of undetermined origin
Ulcerative colitis
Duplications of the colon
Intussusception when not an emergency
Imperforate anus, when elective after the neonatal period

qualitative and quantitative aerobic and anaerobic bacteriologic techniques. From a comparative evaluation of the various drugs studied under standardized conditions of hospital care, drug administration and bacteriologic analysis it has been possible to compare the efficacy of the various agents. It is thought that the study of these agents under such standardized conditions in the same laboratory provides for more valid comparisons than does the comparison of drugs tested in different laboratories under different standards of treatment and bacteriologic analysis.

On the basis of the study of over 35 different drugs, drug combinations and drug dosages it has been possible to divide the agents into those that are and those that are not suitable for intestinal antisepsis (Table 42). Experience with these drugs led to further subdivision of the recommended drugs into special categories for those that are specially recommended for children because of the peculiar response of the flora in children.

Drugs in the Not Recommended category fail to control the bacterial

TABLE 42. *Intestinal Antisepsis*

NOT RECOMMENDED	
Chloramphenicol	Ristocetin
Chlorquinaldol	Sulfasuxidine
Clorpactin WCS-90	Sulfathalidine
Colymycin	Tetracycline
Erythromycin	Chlortetracycline
Furoxone	Oxytetracycline
Hexetidine	Tetracycline
Novobiocin	Tetracycline V
Penicillin V	Zirconyl tetracycline
Phenoxyethyl penicillin	Tetracycline-nystatin
	Thiostrepton
INTERMEDIATE	
Chlorquinaldol-neomycin	
Neomycin	
Oxytetracycline	
RECOMMENDED	
General Use	*Special Use*
Bacitracin-neomycin	Erythromycin-neomycin
Kanamycin	Novobiocin-neomycin
Polymyxin B-neomycin	Ristocetin-neomycin
Sulfathalidine-neomycin	Tetracycline-neomycin
Thiostrepton-neomycin	
Pediatric Use	
Amphotericin-neomycin	
Nystatin-neomycin	

flora of the large intestine, are often associated with undesirable side reactions, are rapidly absorbed from the gastrointestinal tract and therefore are not available for effective action in the colon, and are widely used for many other purposes and therefore would be more likely to be used in patients with a pre-existing resistant flora.

The second group are intermediate in their activity.

Those drugs recommended for special use are highly effective in controlling the bacterial flora of the stool, but have the disadvantages of being combinations with neomycin of drugs that are rapidly absorbed from the gastrointestinal tract and are widely used for other conditions. Specific indications for these combinations are as follows: the treatment of any patient who acquires a staphylococcal infection of the gastrointestinal tract, the preoperative preparation of any patient who might be expected to have a resistant gastrointestinal flora because of prolonged antibacterial therapy for some other condition, and for the treatment of a postoperative or postantibiotic diarrhea.

The drugs recommended for general use and those recommended specially for children all have been shown to be particularly effective in the control of the bacterial flora of the stool by the techniques used in this laboratory. All but one are combinations with neomycin of

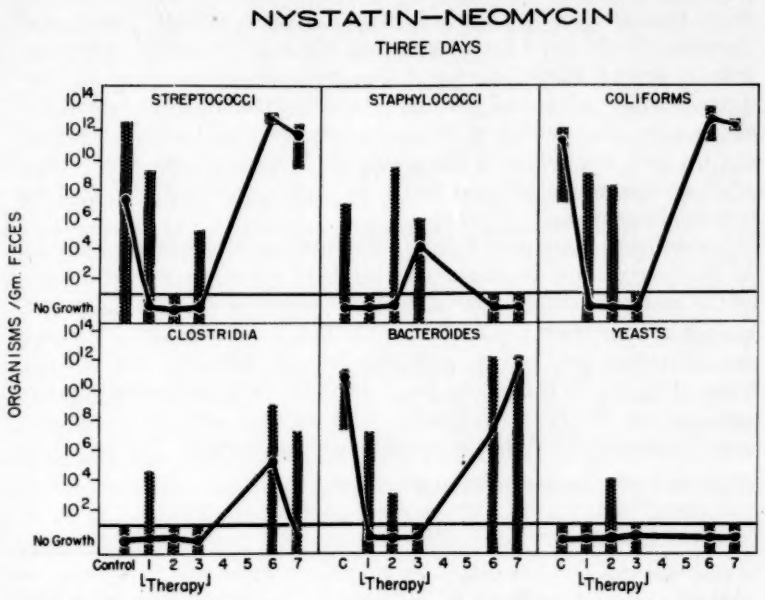

Fig. 28. Response of fecal flora to nystatin-neomycin routine in adults. Bars indicate range of counts, and solid line indicates median count. Note the absence of yeast proliferation during the time the majority of the bacterial flora was well controlled.

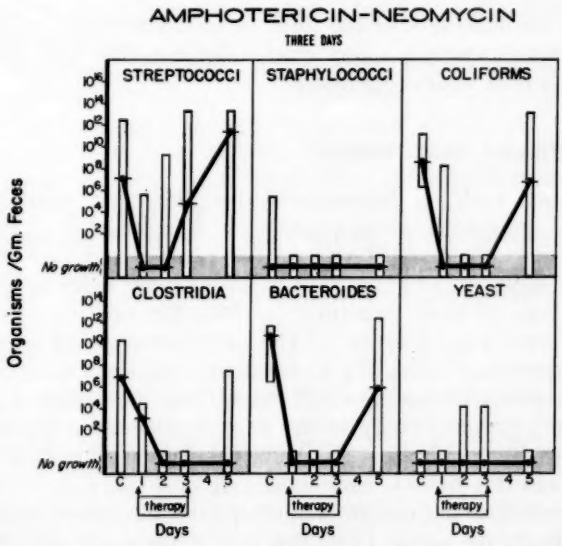

Fig. 29. Response of fecal flora to amphotericin-neomycin in adults. Chart plotted in same fashion as Figure 28.

drugs that are poorly absorbed from the gastrointestinal tract, and therefore should exert their maximum effect in the colon, where activity is desired. Partly because of their poor absorption, none of these drugs is widely advocated for oral administration, and this lessens the chances for development of resistant gastrointestinal bacteria. Kanamycin, the only single drug in the group, has become the standard on our adult service, and is believed to be the most effective single agent for intestinal antisepsis.

Nevertheless none of the drugs just listed are recommended or used in the preoperative preparation of children, because adequate control of the gastrointestinal bacterial flora of children leads to a rapid overgrowth of troublesome yeast forms. For this reason we have adopted a special routine for children, and have had no difficulty with this program (Figs. 28, 29). If neomycin is combined with an antifungal drug such as nystatin or amphotericin, both bacteria and yeasts are adequately controlled.[5] With the nystatin-neomycin routine (Table 43) we

TABLE 43. *Nystatin-Neomycin Routine for Intestinal Antisepsis*

AGE	DRUG		TIME SCHEDULE
6 years and above (Adults)	Nystatin	250,000 units	Every hour for 4 hours, then every 4 hours for 72 hours
	Neomycin	1.0 gm.	
3–6 years	One-half adult dosage at each time interval		
1–3 years	One-third adult dosage		
Up to 1	One-fourth adult dosage		

have had no difficulties in the form of yeast complications, diarrhea, gastrointestinal upsets, nor any other difficulties that have led to dissatisfaction with intestinal antisepsis.

INTRAPERITONEAL DRUG THERAPY

Experimental work has demonstrated the efficacy and safety of intraperitoneal kanamycin administration in the presence of extensive intraperitoneal infection.[7] Review of the literature[4] indicates that intraperitoneal antibiotic administration would be more widely used if there had not been so much dissatisfaction with the side reactions to the intraperitoneal administration of the early antimicrobial agents. Following experimental studies with intraperitoneal kanamycin, a clinical study was instituted, and over 120 patients have now received kanamycin in the peritoneal cavity at the time of operation. The results of this study have indicated the value of intraperitoneal kanamycin therapy, and this study is continuing.

Intraperitoneal kanamycin administration has been used in 18 patients under the age of 12 on this service, using 500 mg. either as a

powder or dissolved in 10 to 25 cc. of saline. The youngest patient to receive intraperitoneal kanamycin was a seven-day-old infant with a perforation of the splenic flexure of the colon. The principal indication has been for perforated appendicitis, as might have been anticipated from Spencer's[10] observation of 75 cases with a perforated appendix among the 174 cases of appendicitis in 5 years on the L.S.U. Pediatric Surgery service. It was not expected that intraperitoneal kanamycin would completely eliminate complications, but the fact that 6 of the 12 patients with perforated appendicitis did not have any complications is indicative of the place that such drug usage might have.

In addition to its use in ruptured appenditicis, intraperitoneal kanamycin would seem to have a place under the following conditions: peritonitis of any etiology, intra-abdominal abscess, ruptured abdominal viscus following blunt or penetrating injury to the abdomen, rectal injuries which involve lacerations of the bowel wall above the peritoneal reflection, intestinal obstruction with gangrenous bowel, or any emergency procedure in which undue contamination of the peritoneal cavity occurs. It should not be necessary to indicate that appropriate surgical measures must accompany any such use of antibiotics.

SUMMARY

Preoperative intestinal antisepsis for lesions of the colon has a place in pediatric surgery just as it does in adult surgery, provided there is appreciation of the different response of children to this form of antimicrobial therapy.

Yeast overgrowth is more rapid and more troublesome in pediatric than in adult practice, and effective antifungal therapy must be combined with antibacterial therapy for optimum results.

A comparative study of antimicrobial agents for intestinal antisepsis has indicated which ones are satisfactory, and clinical experience has confirmed these findings.

Intraperitoneal kanamycin administration has demonstrated its safety and value in various types of peritoneal contamination, and its use is advocated in surgical problems with extensive peritoneal soiling.

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ANTIMICROBIAL THERAPY OF GENITOURINARY TRACT INFECTIONS

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The past several years have seen much work and advance in the treatment of the infected kidney and its associated structures. From the list of the newer antimicrobials several have been drawn for treating the infected urinary tract. Current use of methionine for urine acidification has brought about greater effectiveness of mandelic acid therapy, first introduced by Rosenheim of London a quarter of a century ago. Diagnosis, the handmaid of therapy, has been made more certain by the quantitative urine culture. Together, the efforts of the radiologist and the urologist have given us better definition and treatment of associated anatomic defects. Included among these is the delineation of vesico-ureteral reflux, a not uncommon cause and consequence of the urinary tract infection of the child and of even the adult.

URINARY TRACT INFECTION AND ASSOCIATED PATHOLOGY

Urinary tract infection in the female patient is frequently unassociated with anatomic or functional pathology, particularly in the first infection. In the male patient, however, urinary tract infection often means that a pathologic state is present and that early urologic investigation is required. As a minimum, the investigation should include observation of micturition, excretory urography and a delayed cystogram. According to Campbell,[1] the lower urinary tract conditions that most commonly lead to an infected urinary tract are hypertrophy of the verumontanum, congenital valves of the prostatic urethra, neuro-

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muscular dysplasia of the bladder, stenosis of the prepuce or meatus, and ureteral stricture. Upper tract lesions most commonly found are ureteral stricture (more than 50 per cent of all upper tract lesions), ureterocele, ureteral duplication, obstruction due to aberrant vessels, ureteral kinks and periureteral bands, and renal calyx stricture.

Vesico-ureteral reflux of urine as an entity has been known for over 50 years.[30] The chance observation by Stewart,[23] first made in 1948, that a delayed cystogram delineated the presence of vesico-ureteral reflux has led to the routine use of this technique in the past few years. There is general agreement today that vesico-ureteral reflux is always pathological and in some instances may be either the cause of urinary tract infection or in others the result of it. According to Ericsson,[4] in as much as one third of cases of urinary tract infection vesico-ureteral reflux is present. Infection and reflux set in motion a vicious circle, and treatment must be directed at the physiologic and anatomic factors involved.[18, 24] Hodson and Edwards[7a] describe its clinical and radiologic appearance and the technique for its demonstration.

DIAGNOSIS

Although classic symptoms and findings of urinary frequency, dysuria, flank or abdominal pains, chills and fever point to urinary tract infection, ultimately the diagnosis requires study of the urine. Direct staining of the urine in urinary tract infections will often reveal the presence of bacteria, but therapy with a minimum risk for the patient requires that the urine be cultured, and sensitivity tests performed.

Collection of the Urine Specimen

A standardized method of urine collection should be used. In the female child who is able to cooperate the following procedure is recommended.[26] The perineum is scrubbed with a cleansing agent such as pHisohex for two to three minutes. The labia are separated, and the vulva is washed first with a cleansing agent and then with 1:1000 Zephiran, using downward strokes and a fresh cotton swab for each stroke. The first few cubic centimeters of the urine are discarded, and the free-flowing urine is collected in a sterile test tube. Often, however, it is necessary to affix a collection tube to the patient when immediate voiding is impossible.* If the urine is not cultured immediately, it should be refrigerated. Culture is preferable within a few hours, but the urine can be stored overnight. For the younger patient catheterization or even, at times, percutaneous suprapubic needle aspiration of the bladder

* For this purpose a sterile plastic tube such as the Pediatric Urine Collector, Sterilon Corporation, Buffalo, New York, is useful.

needs to be used.[23, 27] In the cooperative male child midstream urine collection after cleansing the glans and prepuce is recommended.

Quantitative Urine Culture

Difficulty in distinguishing the contaminant from the significant organism in the urine and the desire to avoid catheterization have led to the adoption by many of the technique of quantitative culture of the "clean-voided" specimen. With brief experience the quantitative technique proves to require little more time and effort than the so-called routine culture. Briefly, one procedure consists in preparing a 1:100 dilution of urine* by mixing 0.1 cc. of urine with 9.9 cc. of sterile saline. A trypticase-soy agar pour plate is made from 0.1 cc. of the diluted urine; colonies are counted the following day. Each colony counted represents 1000 organisms per cubic centimeter of the original urine when the outlined procedure is followed. At the time that the "pour" plate is prepared, blood agar and EMB streak plates and thioglycolate tubes are inoculated for eventual identification and sensitivity tests, and detection of anaerobic organisms.

According to their studies in children, Pryles et al.[26, 27] indicate that bacterial counts above 100,000 per cubic centimeter of urine are indicative of infection; counts below 1000 colonies mean no urinary tract infection; while counts between these limits suggest the possibility of infection, requiring further investigation and repeat cultures. Using a "spread plate" technique, Hinkle, Partin and West[7] found that over 3000 colonies per cubic centimeter were significant of urinary tract infection in children. These authors were of the opinion that colony counts of 10,000 per cubic centimeter using the pour plate method are significant of urinary tract infection in children.

Pyuria

Despite the frequent coincidence of pyuria and bacteriuria, one may exist without the other. The coincidence of these two is greater in acute than in chronic infections. Staffron and Engel[32] find an 84 per cent coincidence of these in acute urinary tract infections. By considering 5 white blood cells per high-power field in the centrifuged specimen indicative of pyuria, Kass[10] notes the simultaneous presence of bacteriuria and pyuria in 33 to 50 per cent of cases. Of the patients having less than 1000 colonies per cubic centimeter, only 2 per cent had a pyuria. Or, to state this in another way, bacteria can more often be found

* In the adult the first morning "clean catch" or four-hour interval urine is used. The urine from the child should approximate either of these whenever feasible. Counts lower than those specified may be indicative of infection if the urine is from a shorter collection period.

without pus cells than pus cells can be found without bacteria. Often, soon after institution of therapy, pyuria may disappear, though bacteriuria is still present. Therefore reliance on the disappearance of pus cells from the urine as evidence of eradication of infection will be misleading. Winberg and Barr,[34] in following up 33 children with urinary tract infection, found a persistent bacteriuria in 14 despite the disappearance of pyuria, urinary symptoms and return of the sedimentation rate to normal. The presence of pyuria in the absence of significant bacteriuria should direct the physician's attention to the possibility of an unrecognized glomerulonephritis, genitourinary tuberculosis, lupus erythematosus, sarcoid or lymphoma.[22] Chronic pyelonephritis may also demonstrate on occasion an elevated urine white blood cell count without consistent bacteriuria (see section on pyelonephritis).

THE BACTERIAL FLORA

Pryles[25] surveyed a group of urinary tract infections in children and found that 92 to 94 per cent were due to gram-negative bacilli and 6 to 8 per cent to gram-positive cocci. Seventy-five per cent of acute, untreated urinary tract infections were due to a single organism. Of the bacilli, *Escherichia coli* is the most common.[5, 9, 25, 28] Proteus, Aerobacter and Pseudomonas are found to be the next most common, in that order. By some, Aerobacter is found more commonly than Proteus.[20, 31] *Staphylococcus aureus* and then the enterococcus are the most common of the gram-positive organisms. Since these pathogenic agents are also the most frequent to contaminate a urine specimen, there is a growing reliance on quantitative urine bacteriology for the diagnosis of urinary tract infection.

Infections with more than one organism, or mixed infections, are found most commonly in the chronic infections and suggest the presence of background abnormality. These mixed infections most commonly involve association of *E. coli* and the enterococcus.[5, 28] Next most often *E. coli* and Proteus are associated; Proteus and Pseudomonas are also frequently associated. Gardborg,[5] in investigating 108 cases of urinary tract infection, found that 10 per cent had mixed flora before therapy and 32 per cent had mixed flora if the therapy was unsuccessful. Although *E. coli* was the most common organism before therapy, the most common organism that emerged after unsuccessful therapy was Proteus. Sometimes after successful eradication of one organism, the appearance or uncovering of a new organism occurred. In reviewing over 1000 cases of urinary tract infection in children and adults, Rhoads[28] observed that a new organism had appeared in one fourth of the unsuccessfully treated cases. Marshall and Johnson[21] found that a change in organism occurred in 28 per cent of

recurrent infections in patients free of urologic complications. In the cases with urologic complications there was a change in bacterial flora in 42 per cent of the cases.

ANTIMICROBIAL AGENTS

The choice of the antimicrobial agent will depend on sensitivity tests and other considerations. Acute cystitis in the female responds so often to "the course of sulfonamides" that there can be little argument with such routine practice, provided there is also practiced the routine of culturing the urine after cessation of therapy. When immediate therapy is demanded by the severe infection, the Gram stain may determine the choice of the antibacterial agent, while later culture and sensitivity tests may alter the choice. Toxicity and the frequent emergence of insensitive organisms may restrict some of these agents to short-term use only.

In the main, dose of these agents for urinary tract infections will be that used for general purposes. Exceptions will be noted. Agents principally excreted by the kidney may accumulate to toxic levels rapidly with standard drug dosage when renal insufficiency is present,[13, 15, 16] while urinary concentrations may decline to ineffective levels. The latter circumstance may especially prevail when drug dose is reduced to avoid the hazard of toxic levels and additional kidney damage. These considerations at times present to the therapist an insoluble dilemma.

The therapeutic agent should be given beyond the first appearance of a sterile urine in the quantitative sense. A change in drugs may be required. How long the period of drug administration should extend beyond the first sterile urine depends more on the therapist's judgment than on any dictum. In general, the chronic or recurrent infection will have a longer period of therapy beyond the first sterile urine (if ever this is attained) than the acute infection. Culturing the urine at intervals after interruption of therapy is a guide. For the infection that is persistently recurrent, continuous therapy may be required.

Mandelic Acid

The introduction of methionine[11] for effective acidification of the urine has led to greatly renewed use of mandelic acid for urinary tract infections. Mandelic acid is a keto acid which is excreted without change in the urine. Its original selection by Rosenheim[29] in 1935 derived from the observations that a ketosis was often followed by improvement of urinary tract infections. Mandelic acid is frequently effective against a variety of organisms, including *E. coli*, Proteus,

staphylococcus, enterococcus and Pseudomonas. An acid pH is required for its action, and until recently this was difficult to achieve in many cases of urinary tract infections. Too often ammonium chloride was ineffective, presumably because of urea-splitting organisms and rapid renal acid-base readjustments. Methionine, a sulfur-containing amino acid, is metabolized, leaving the acid sulfate radical for excretion. In the adult, 12 to 15 gm. per day will provide urinary acidification to pH 5, an ideal range for the action of mandelic acid. Methionine generally produces an unpleasant body odor and has a disagreeable taste. Mandelic acid may produce nausea and vomiting. Hematuria in 2 per cent of cases has been noted by Kleeman, Hewitt and Guze.[12] Restriction of fluids necessary to bring about adequate urine concentration of mandelic acid of 0.25 to 1.0 gm. per 100 cc. of urine, and the acid load contraindicate the use of this combination of drugs in acute pyelonephritis and in situations in which renal insufficiency exists. This drug combination deserves consideration in lower urinary tract infections, in chronic infections in the absence of renal insufficiency, and for the long-term suppressive therapy of intractable chronic infections associated often with anatomic defects.

Sulfonamides

These compounds are very effective against *E. coli* and at times against the cocci except for the enterococci. On rare occasions they are effective against Aerobacter, Proteus and Pseudomonas. The effect in vivo against these latter organisms does not match the action in vitro. The newer derivations such as Gantrisin, Thiosulfil, Sulamyd and Elkosin have greater solubility than the individual sulfapyrimidines such as sulfadiazine. But their acetylated derivatives, which appear in the urine, are less soluble than the free forms, and present the hazard of precipitation unless good fluid intake is maintained during their use. These compounds still have much value in the treatment of acute and chronic infections, and in suppressive therapy.[17, 22]

Penicillin

Although its use is not often indicated in the treatment of urinary tract infection, penicillin may be the agent of choice in the occasional sensitive coccus infection. Gram-negative organisms do not generally fall within the antibacterial spectrum of penicillin; nevertheless Daikos[3] found that of 250 strains of gram-negative organisms isolated from urinary tract infections, 72 were sensitive to it. Penicillin used in combination with streptomycin is effective in some enterococcal and staphylococcal infections.

Streptomycin

In spite of its wide use, streptomycin should seldom, if ever, be used in a urinary tract infection without indication of organism sensitivity. It is frequently effective against *E. coli* and at times (infrequently) against Aerobacter-Klebsiella, Proteus and Pseudomonas. In a given instance of the latter type of infection it may be the least toxic of the choice of effective agents. Because of this and because bacterial resistance to the drug often develops rapidly, Kleeman, Hewitt and Guze[12] suggest that streptomycin be selected for use only when the potentiality for the cure is best. Associated urologic problems should be attended to first before this drug is used. Obstructive uropathy, granulating surfaces, catheters, or other foreign bodies which preclude bacteriologic cure, are contraindications to its use, since the emergence of resistant strains is certain. Hewitt, Stone and Finegold[6] recommend in the case of sensitive strains of *Proteus mirabilis* combination of this drug with penicillin, and in the case of sensitive strains of *Proteus vulgaris*, streptomycin combined with chloramphenicol. Hewitt[12] calls attention to the effectiveness of streptomycin and penicillin in urinary tract infections due to enterococci and staphylococci. The antibacterial activity of streptomycin is greatly increased in the presence of an alkaline pH; therefore concomitant alkali therapy is advocated in order to maintain a urine pH of at least 7.5 during streptomycin therapy.

Eighth nerve damage may occur even with small doses of streptomycin. Nephrotoxicity may occur particularly if renal pathology preexists. Excretion of streptomycin is decreased in the presence of renal insufficiency, and toxic levels may quickly be reached on ordinary dosage schedules.[13]

Chloramphenicol

Reports of the toxic bone marrow effects of chloramphenicol are well known. Careful use of this agent remains justifiable in view of the rarity of this complication as compared with the frequency for the need of this agent. A high percentage of *E. coli* and Klebsiella-Aerobacter are sensitive to it. Frequently, enterococci and other streptococci are also found to be sensitive. Kleeman, Hewitt and Guze[12] point out that the somewhat restricted use of this agent doubtless accounts for the continued sensitivity of many organisms. Except in those infections acquired in the hospital, urinary tract infections due to the Staphylococcus generally respond to chloramphenicol. Pseudomonas and Proteus are infrequently sensitive to this agent. Although 75 to 90 per cent of the administered dose may be recovered in the urine of patients who have normal renal function, only 5 to 15 per cent of the

recovered drug is in the active form. Consequently, for effective treatment of urinary tract infections, doses two or more times greater than those used for other infections may be required in order to achieve adequate antibacterial concentrations in the urine.

Tetracyclines

Chlortetracycline (Aureomycin), oxytetracycline (Terramycin), tetracycline and demethylchlorotetracycline (Declomycin) often show relative differences in antibacterial effect, and therefore individual sensitivity tests are required. Their clearance rates by the kidney differ, so that the ultimate urine concentration attained by each member for a given drug dose will be different. In part, these differences are due to differences in plasma protein binding. The excretion rates for these compounds are Terramycin>tetracycline>Declomycin>Aureomycin.[14] In general, members of this group are effective against *E. coli*, Aerobacter-Klebsiella and Bacterioides. Their best use is in the acute type of infection, including the nonhospital-acquired Staphylococcus, as well as in the short-term therapeutic attempt in chronic or recurrent infections. Long-term therapy using one of these agents is advised against because of the frequent emergence of resistant strains or the development of fungus or the ominous staphylococcal enteritis. Studies by Kunin, Rees, Merrill and Finland[16] indicate retention of tetracycline with rising blood levels in renal insufficiency when the endogenous creatinine clearance is reduced to 30 cc. per minute.

Nitrofurantoin

The antibacterial spectrum of nitrofurantoin (Furadantin) is broad and includes strains of *E. coli*, *A. aerogenes*, *K. pneumoniae*, *Streptococcus viridans*, enterococci and staphylococci. Some species of Proteus are susceptible, while others are highly resistant. Almost all species of Pseudomonas are resistant. Although susceptible strains seldom acquire resistance to the drug and urinary sterilization is achieved in a good percentage of infections, relapse after cessation of therapy may occur. As with mandelic acid therapy, the concomitant use of methionine may be necessary in order to maintain an acid urine pH, particularly when a urea-splitting organism such as Proteus is present.

Marshall and Johnson[21] used this compound in 100 children with chronic and recurrent urinary tract infections. Twenty-eight had associated anatomic pathology, 72 were without abnormality. On a dosage of 6 to 10 mg. per kilogram, 36 of the patients with uncomplicated cases had bacteriologic cure, but in 24 of these there was recurrence of infection on cessation of therapy. Suppression of the infection

on reinstitution of therapy occurred in the latter cases. Three of the 72 uncomplicated cases had no benefit from therapy. Eight of the 28 patients with anatomic abnormality had bacteriologic cure, 12 of the 28 were uncontrolled, and the remainder had some control of infection with continuous therapy.

Side effects of therapy with nitrofurantoin include nausea and vomiting, diarrhea, headache, skin rashes and fever. A few cases of hematologic complications have been reported.

Polymyxin B

Properly used with adequate regard for potential toxicity, polymyxin is an excellent agent for the treatment of many difficult urinary tract infections. It is the most proved agent against the Pseudomonas, and at times it is the only agent effective against *E. coli* and the Aerobacter-Klebsiella group. Hewitt[12] advocates that the usual intramuscular dose of 2.5 mg. per kilogram every 8 hours be reduced to 1.0 to 1.5 mg. per kilogram per 24 hours in the presence of renal insufficiency (though such reduction is mandatory, the therapist must realize the decreased potential effectiveness of the agent with the greatly reduced clearance of it in such circumstances).

Side effects of the drug may be dizziness, ataxia, manifestations of peripheral neuritis, paresthesia—particularly of the face—itching, facial flushing and fever. According to Hewitt, these symptoms disappear 24 to 72 hours after discontinuance of the drug.* Renal toxicity, as manifested by proteinuria, the appearance of cells and casts, and nitrogen retention, according to Hewitt, is reversible. Doubtless some reports of permanent renal damage stem from the practice of resorting to this agent after considerable delay in time and all else had failed. The experience of Hewitt and others suggests early resort to polymyxin in serious Pseudomonas infections and other infections in which sensitivity tests call for its use.

Colymycin

Colymycin has been recently studied in the therapy of urinary tract infections. Because of an apparent lack of kidney toxicity and an antibacterial spectrum resembling that of polymyxin B, great interest is shown in its use for the treatment of Pseudomonas infections. It is a polypeptide complex with two organic oxyacids. Recommended dosage is 1.5 to 5 mg. per kilogram per day in 3 to 4 divided doses. The

* These symptoms may be prevented or relieved by administration of antihistamines (see B. M. Kagan, D. Krevsky, Milzer and M. Locke: *J. Lab. & Clin. Med.*, 37:412, 1951).

drug is not absorbed in appreciable quantity from the gastrointestinal tract. Wright and Welch[35] noted that the maximum bacterial concentration in vitro required against Pseudomonas, Aerobacter and *E. coli* was 2.4 micrograms per milliliter. With adequate kidney function, 20 or more times this required maximum urinary concentration is achieved on routine dosage. Pseudomonas was eradicated in urinary tract infections, according to Carroll and Mallette,[2] but in 16 of these patients, Proteus, against which this agent is ineffective, appeared. McCabe et al.[19] report significant bacteriologic response in 62 per cent of urinary tract infections treated with this agent. Side effects of its use include parasthesias, and nausea and vomiting. Granulocytopenia has been noted in some patients receiving this drug. It is not certain, however, that the toxic effect was due to this agent or to other concurrently used antimicrobial drugs.

Kanamycin and Neomycin

In serious urinary tract infections not susceptible to other antimicrobial agents, the use of kanamycin or neomycin should be considered. The potential serious side effects make it advisable that these compounds be used only in the hospital. The two drugs have similar antibacterial spectra and are frequently effective against Proteus, Aerobacter and *E. coli*. Organisms resistant to one agent are always resistant to the other. Frequently, bacteria which become resistant during streptomycin therapy are found to be resistant to these agents.

Serious toxic reactions limit the usefulness of these compounds. Hearing loss or high and intermediate tone deafness may develop within but a few days of therapy or may not appear until one or two weeks after cessation of therapy. Kidney damage as manifested by albuminuria, casts and red cells, as well as nitrogen retention, may occur within one week on moderate dose schedules. Therefore the use of these agents must be monitored with frequent urinalysis and blood urea nitrogen determinations. Drug retention occurs with renal impairment and increases, therefore, the hazard of ototoxicity. Although renal damage may show apparent reversibility, hearing loss is permanent. Yahiro and Rosenthal[36] studied the use of kanamycin in 20 children, ages 3 months to 13 years. Thirteen infections were acute, seven were chronic. In 12 of the acute and 4 of the chronic infections the urine was rendered sterile.

Novobiocin

Staphylococcal and Proteus infections resistant to other antimicrobials may require the use of novobiocin. On rare occasions it has been used

in other coccal infections. Only a small proportion of the administered drug reaches the urine, but adequate therapeutic levels are possible with oral or parenteral administration. Results with this drug are irregular. There is recurrence of Proteus infections, at which time the organism, often, is resistant. Side effects include drug dermatitis; hepatic involvement has been noted, but may be questionable. It is one of the least effective antimicrobial agents for urinary tract infection.

Cycloserine

The antituberculous drug cycloserine has been recently used in urinary tract infection by Hughes, Coppridge and Roberts.[8] Chronic infections due to *E. coli* and Aerobacter responded, while those due to Pseudomonas and Proteus did not.

URINARY TRACT INFECTION AND PYELONEPHRITIS

The tragic course of progressive pyelonephritis may follow, early or late in life, an unsuccessfully or improperly treated urinary tract infection. The infection may have been from the first a pyelonephritis, or may have led to it.

The principal pathway of antimicrobials through the kidney involves glomerular filtration or tubular secretion. Such events are not conducive to high interstitial tissue concentrations of these agents, particularly in areas of infection. Organisms may persist in foci within the kidney remote from the main stream of the antimicrobial agent. The intermittency of the bacteriuria in some cases of pyelonephritis doubtless represents the occasional entrance into the tubular lumen of organisms from such foci.

From the experience of Kass[10] and others, we may expect to encounter low bacterial colony counts in occasional cases of pyelonephritis. Repeat urine cultures may provide the most likely organism or organisms involved. Antimicrobial therapy is then indicated, but if a measure of renal insufficiency has developed, the likelihood of achieving effective urine or kidney tissue concentration of the agent for a sterilizing effect becomes remoter than before.

Clearly, the most effective therapy of pyelonephritis is the early adequate treatment of each urinary tract infection.

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PEDIATRIC DOSAGES, ROUTES OF ADMINISTRATION AND PREPARATION PROCEDURES FOR PARENTERAL THERAPY WITH ANTIMICROBIAL AGENTS

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PEDIATRIC DOSAGES AND ROUTES OF ADMINISTRATION

Tables 44 and 45, at the end of this clinic, present dosages and routes of administration.

PREPARATION PROCEDURES FOR PARENTERAL THERAPY

The following presents a useful and abbreviated guide. For more detailed information refer to company literature usually supplied with each drug.

Amphotericin B

Amphotericin B is prepared by adding 10 ml. of dextrose for injection (5 per cent U.S.P.) to the 50-mg. powdered vial. The solution is then further diluted with the same diluent to a concentration of 0.1 mg. per milliliter (1 mg. per 10 ml.). The solution is usually given once daily by intravenous drip over a six-hour period. It may be given every other day if symptoms of toxicity appear. The vials should not be exposed to sunlight. The reconstituted solution should be discarded after 24 hours.

Bacitracin

Bacitracin may be given by intramuscular or intrathecal route. For intramuscular use, 5 ml. of 2 per cent procaine in sodium chloride solu-

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tion is added to the 50,000-unit vial. This provides a concentration of 10,000 units per milliliter. If it is not given deep intramuscularly, superficial ulceration may result. For intrathecal administration, procaine solution is contraindicated. For intrathecal use the 50,000-unit vial should be diluted with 50 ml. of sterile sodium chloride, to provide a concentration of 1000 units per milliliter. Bacitracin solutions should be refrigerated and discarded after one week.

Chloramphenicol

Chloramphenicol succinate may be administered by intravenous, intramuscular or subcutaneous route. For intravenous and subcutaneous administration a 10 per cent solution is recommended. For intramuscular use a 25 per cent solution is advised. The 10 per cent solution is prepared by adding 11 ml. of sterile water or 5 per cent dextrose to the 1-gm. vial. The 25 per cent solution is prepared by adding 4 ml. of the same diluent to the 1-gm. vial. The drug may be given as a constant intravenous drip, or as single injections over a one-minute interval. When it is given as a single intravenous dose, blood levels are maintained for a six- to eight-hour period. Chloromycetin solutions are stable at room temperature for one month.

Colymycin

Colymycin (sodium colistin methanesulfonate) is supplied in a vial containing 150 mg. of the powder for intramuscular use. Intravenous use is not recommended. The vial should be diluted with 2 ml. of sterile U.S.P. water and is to be administered in 2 to 4 doses. The reconstituted solution should be used within 24 hours after preparation.

Erythromycin

Erythromycin (Ilotycin, Erythrocin) may be given intravenously. Intramuscular use is not advised. For intravenous preparation, 10 ml. of sterile water should be added to a 250-mg. ampule. This provides a concentration of 25 mg. per milliliter. This solution is then added to 100 ml. of sodium chloride or 5 per cent dextrose water and given within a 1- to 2-hour period. This procedure should be repeated at six-hour intervals.

Furadantin

Furadantin (nitrofurantoin) is prepared by adding 15 ml. of sterile water to a 180-mg. vial. This provides a concentration of 12 mg. per milliliter. Each milliliter is then further diluted to 33 ml. of a standard intravenous solution. The drug is then administered as a constant intravenous drip, and is usually given at 12-hour intervals.

Kanamycin

Kanamycin sulfate is available in 500-mg. (2-ml.) and 1-gm. (3-ml.) vials. Intramuscular administration is preferred to the intravenous route. When the intravenous route must be used, the vial is diluted with standard intravenous solutions so as not to exceed a concentration of 2.5 mg. per milliliter. It should then be given as a slow intravenous drip. Kanamycin should not be combined with Staphcillin, since reports indicate that these two drugs inactivate each other.

Kanamycin may also be given by aerosol, 250 mg. 2 to 4 times a day. One milliliter of a 500-mg. vial should be diluted with 3 ml. of sterile saline and nebulized. Kanamycin has also been used as an irrigating solution for abscess cavities, in both the pleural and peritoneal spaces. The concentration of such a solution should not exceed 2.5 mg. per milliliter.

Neomycin

Neomycin sulfate is prepared by adding 2 ml. of sterile sodium chloride to a 500-mg. vial. Doses of 1 ml. or less are recommended for intramuscular use at 6-hour intervals. The prepared solution should be discarded after 72 hours. This drug should not be given intravenously. Neomycin may be given by aerosol by adding 10 ml. of normal saline to the 500-mg. vial. Two milliliters (50 mg. per milliliter) is combined with 2 ml. of Alevaire or Isuprel and administered 4 times daily. For adults 500 mg. of a 1 per cent solution in saline may be injected into the pleural cavity, or given as an intra-articular injection. The drug is not recommended for intraperitoneal administration, since apnea, cardiac arrest and respiratory distress have occasionally resulted.

Novobiocin

The intravenous solution is prepared by diluting a 500-mg. ampule with 10 ml. of sterile sodium chloride. This solution is further diluted with 250 to 500 ml. of normal saline if a constant intravenous drip is desired. When administered as a single injection, novobiocin is given in a concentration of 10 to 15 mg. per milliliter. Slow intravenous drip is preferred. Novobiocin should not be given intravenously with any glucose-containing solution. For intramuscular use the ampule may be reconstituted with either sterile saline or water. The parenteral solution is unstable and should be discarded immediately after use. Novobiocin does not diffuse into the spinal fluid and should not be used for the

treatment of meningitis. The intrathecal use of the drug is contraindicated.

Oleandomycin

Oleandomycin phosphate may be administered intravenously or intramuscularly. For intravenous use, 10 ml. of U.S.P. water should be added to a 500-mg. ampule. This should be further diluted by adding 5 per cent dextrose water, or saline in a concentration not to exceed 2 mg. per milliliter. For intramuscular use 7.5 ml. of 1 to 2 per cent procaine solution is added to the vial, making a concentration of 100 mg. per 1.5 ml. Procaine should not be used intravenously. The drug should be given deep intramuscularly. It may be safely stored at room temperature for four weeks.

Penicillin G

Penicillin G may be administered by intramuscular or intravenous route. The vial may be diluted with sterile water or normal saline in varying dilutions. Penicillin may be given in standard intravenous solutions. The recommended concentration has been as high as 1000 units per milliliter, although higher concentrations have been given. Care should be exercised to prevent potassium intoxication when administering large intravenous doses *to young infants*. For example, 20 million units of potassium penicillin G will contain 1.3 gm. of potassium, or 33 milliequivalents. When large doses of intravenous penicillin are necessary, a sodium preparation should also be utilized. Penicillin solutions may be stored in the refrigerator for one week after reconstitution.

Polymyxin

Polymyxin may be given by intramuscular or intrathecal route. Local pain and parethesias are 2 common complications that can be minimized by decreasing the interval between intramuscular doses to 4 to 6 hours and thereby reducing the individual dose. To further reduce local pain, the 50-mg. vial should be diluted with 10 ml. of 1 per cent procaine hydrochloride, providing a concentration of 5 mg. per milliliter. Polymyxin does not cross the normal blood-brain barrier. Procaine is contraindicated for intrathecal therapy. Therefore, for intrathecal use, 50 ml. of normal saline should be used as the diluent, and the solution injected in a concentration of 0.5 to 1.0 mg. per milliliter. In endocarditis it has been given intravenously in a concentration of 0.4 mg. per milliliter in 5 per cent dextrose solution.

Ristocetin

The 500-mg. ampule can be diluted with standard intravenous solutions so as not to exceed a concentration of 2 mg. per milliliter. The drug is given intravenously within a 30- to 60-minute period at 8- to 12-hour intervals. The solution can be stored in the refrigerator for one month without loss of potency.

Sodium Dimethoxyphenyl Penicillin (Staphcillin, Dimocillin)

For intramuscular use the 1-gm. vial should be reconstituted with 1.5 ml. of sterile water or normal saline. This provides a concentration of 500 mg. per milliliter. For intravenous use 50 ml. of sterile saline is added to the reconstituted vial, and the solution is injected at the rate of 10 ml. per minute at 4- to 6-hour intervals. Staphcillin should not be used with kanamycin, since the two drugs may inactivate each other, nor should it be mixed in the same syringe with streptomycin. The reconstituted solution is stable when refrigerated for 24 hours.

Streptomycin

Streptomycin sulfate is supplied as powder in 500-mg. and 1-gm. vials, and as a solution. The solution of streptomycin is contraindicated in intrathecal and intravenous therapy because of the preservative it contains. For intramuscular use the powder can be diluted with sterile water or normal saline. If local pain results, 1 per cent procaine hydrochloride may be used as a diluent. Streptomycin may be mixed in the same syringe with penicillin and given as a single injection without loss of effectiveness of either agent. Recent work suggests that streptomycin should not be mixed in the same syringe with Staphcillin. Streptomycin may be stored at room temperature for four weeks.

Sulfadiazine

The 10-ml. 2.5-gm. ampule is prepared for intravenous use by adding 40 ml. of sterile water, or saline, thus providing a 5 per cent solution. Sulfadiazine should not be mixed with glucose-containing solutions. For subcutaneous administration a 2.5 per cent solution is recommended.

Sulfisoxazole

Sulfisoxazole (Gantrisin) can be administered by oral, intravenous and

subcutaneous route. The drug is packaged in 5-ml. 2-gm. vials, and 10-ml. 4-gm. vials. For subcutaneous administration the 2-gm. vial should be diluted with 45 ml. of sterile water to make a concentration of 4 per cent. The drug can be diluted with standard intravenous solutions when administered by this route. Sulfisoxazole should not be given with protein hydrolysates.

Tetracycline

For intravenous use a 1 per cent solution is prepared by adding 10 ml. of sterile distilled water to each 100 mg. of tetracycline. This solution is further diluted with standard intravenous solutions to produce a concentration of 1.0 mg. per milliliter (0.1 per cent solution). A slow intravenous drip is preferred. Single injections of the 1 per cent solution may be given at the rate of 10 ml. in 5 minutes. For intramuscular use 2 ml. of sterile water or normal saline are added to the 100- or 250-mg. vials. This solution should be stored at room temperature and discarded after 24 hours.

Vancomycin

The 500-mg. ampule is diluted with 10 ml. of sterile water. The solution is then further diluted with one of the standard intravenous solutions so as not to exceed a concentration of 2.5 to 5.0 mg. per milliliter. A constant intravenous drip is preferred, although it can be given as single injections at six- to eight-hour intervals. Vancomycin can be stored in the refrigerator for a two-week period after reconstitution without loss of potency.

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TABLE 44. *Daily Dosage Schedule of Antibacterial Agents for Newborn Infants, Premature and Full-Term**

AGENT	ORAL	INTRAMUSCULAR	INTRAVENOUS
Bacitracin		900-1000 u./kg. in 4 doses	
Chloramphenicol**	25[a]–50[b] mg./kg. in 4 doses	25[a]–50[b] mg./kg. in 4 doses	15[a]–25[b] mg./kg. in 2–4 doses (0.5 mg./ml.)
Erythromycin	20–40 gm./kg. in 4 doses		10–20 mg./kg in 2–4 doses (0.5 mg./ml.)
Kanamycin	50 mg./kg. in 4 doses	4–12 mg./kg. in 2–4 doses	
Neomycin	50 mg./kg. in 4 doses	4 mg./kg. in 4 doses	
Novobiocin**	10–20 mg./kg. in 4 doses	10–20 mg./kg. in 2–4 doses	10–20 mg./kg. in 2 doses
Nystatin	200,000–400,000 u. in 4 doses		
Penicillin	50,000 u./kg. in 4 doses	20,000–50,000 u./kg. in 2–4 doses 50 mg./lb.[c] in 4 doses	20,000–50,000 u./kg. in 4 doses
Polymyxin	10–15 mg./kg. in 4 doses	1[a]–2[b] mg./kg. in 4 doses	
Streptomycin		10–40 mg./kg. in 2–4 doses	
Sulfonamides**	50 mg./kg./day[d] in 2–3 doses		
Tetracyclines	10–20 mg./kg. in 4 doses	6 mg./kg. in 2 doses	6 mg./kg. in 2 doses (1 mg./ml.)

* In general, use smaller doses and shorter intervals between doses in first 2 weeks of life and in presence of renal impairment.

** Avoid during first week of life unless essential.

[a] Premature.

[b] Full-term.

[c] Staphcillin or Dimocillin.

[d] First dose should be doubled.

TABLE 45. *Daily Dosage and Routes of Administration of Antimicrobial Agents*

AGENT	ORAL	INTRAMUSCULAR	INTRAVENOUS
Amphotericin B (Fungizone)			1.0 mg./kg.
Bacitracin		1000 u./kg. in 3–4 doses (10,000 u./ml. in 2% procaine)	
Chloramphenicol (Chloromycetin succinate)	50–100 mg./kg. in 4 doses	50–100 mg./kg. in 2–4 doses (25% solution)	50–100 mg./kg. in 3–4 doses (10% solution)
Coly-Mycin		1.5–5.0 mg./kg. in 2–4 doses	
Erythromycin (Ilosone—oral only; Erythrocin; Ilotycin)	40 mg./kg. in 4 doses		40–50 mg./kg. in 4 doses (0.5–1.0 mg./ml.)
Nitrofurantoin (Furadantin)	6–10 mg./kg. in 4 doses p.c.		6.0 mg./kg. in 2 doses
Furazolidone (Furoxone)	<5 yr., 5 mg./kg. >5 yr., 200 mg./day in 4 doses		
Griseofulvin (Fulvicin; Grifulvin)	<25 kg., 20 mg./kg./day >25 kg., 0.5–1.0 gm./day in 3–4 doses		
Humycin, paromomycin (Humatin)	50–100 mg./kg. in 3–4 doses		
Isoniazid (Nydrazid; Rimifon)	15–20 mg./kg. in 2–4 doses	10 mg./kg. in 2 doses	
Kanamycin (Kantrex)	100 mg./kg. in 4 doses	15 (8–25) mg./kg. in 2–4 doses	15–30 mg./kg. in 2–3 doses (2.5 mg./ml.)
Mandelamine	<5 yrs., 1.0 gm. in 4 doses >5 yrs., 2.0 gm. in 4 doses		
Neomycin (Mycifradin)	100 mg./kg. in 4 doses	10–15 mg./kg. in 4 doses Limit to 10 days	

TABLE 45. *Daily Dosage and Routes of Administration of Antimicrobial Agents (Continued)*

SUBCUTANEOUS	INTRATHECAL	AEROSOL	INTRA-PERITONEAL, INTRA-ARTICULAR, INTRAPLEURAL	ADULT OR MAXIMUM DOSE
				1.5 mg./kg./day
	500–5000 u./day (1000 u./ml.)	20,000–50,000 u./ml.	1000 u./ml.	100,000 u./day Maximum in child, 50,000u./day
50–100 mg./kg. in 2–4 doses (10% solution)			5 mg./ml.	3–4 gm./day Maximum in child, 2.0 gm./day
				5 mg./kg./day
			1 mg./ml.	2.0 gm./day
				Oral—10 mg./kg./day IV—360 mg./day
				400 mg./day
				1.0 gm./day
				2–6 gm./day
				500 mg./day
		2 ml. q.i.d. (25 mg./ml.)	2.5 mg./ml.	Oral—3–4 gm./day 1.0–1.5 gm./day
				4.0–6.0 gm. first day 1.0–3.0 gm./day maintenance
		2 ml. q.i.d. (50 mg./ml.)	2 mg./ml. Avoid peritoneum	Oral—6.0 gm./day IM—1.0 gm./day

TABLE 45. *Daily Dosage and Routes of Administration of Antimicrobial Agents (Continued)*

AGENT	ORAL	INTRAMUSCULAR	INTRAVENOUS
Novobiocin (Albamycin; Cathomycin)	20–45 mg./kg. in 4 doses	15–40 mg./kg. in 2 doses	15–40 mg./kg. in 2 doses
Nystatin (Mycostatin)	<2 yrs., 0.4–0.8 million u. >2 yrs., 1–2 million u. in 3–6 doses		
Oleandomycin (Triacetyl [TAO]—oral only; Cyclamycin—oral only)	<8 yrs., 30 mg./kg. in 4 doses >8 yrs., 0.5–1.0 gm./day in 4 doses	30–50 mg./kg. in 3–4 doses	30–50 mg./kg. in 4 doses (2 mg./ml. or less
Para-aminosalicylic acid (PAS)	200–300 mg./kg. or 2–8 gm./day in 3–4 doses		200–300 mg./kg. o 2–8 gm./day (30 mg./ml.)
Penicillin G: Potassium or sodium	500,000–2,000,000 u. in 5 doses ½ hr. a.c.	20,000–50,000 u.kg. in 4–6 doses	20,000–100,000 u./kg in 4–6 doses
Procaine		100,000–300,000 u./dose 1–4 doses/day	
Penicillin, phenoxymethyl (V-Cillin; Pen·Vee) **Phenethecillin** (Syncillin; Chemipen)	500,000–2,000,000 u. in 4–5 doses		
Benzathine penicillin G (Bicillin; Permapen; Duapen)		600,000 or 1.2 million u. (single injection) q. 15–30 days	
Dimethoxyphenyl penicillin (Staphcillin; Dimocillin)		100 mg./kg. in 4–6 doses	100 mg./kg. in 4–6 doses
Polymyxin B (Aerosporin)	10–20 mg./kg. in 4–6 doses	2.5 mg./kg. in 4–6 doses	2.5 mg./kg. in 3 doses (0.4 mg./ml. 5% dextrose in endo carditis)
Ristocetin (Spontin)			25 mg./kg. in 2–3 doses (2.5 mg./ml.)
Streptomycin sulfate	40 mg./kg. in 4 doses	20–40 mg./kg. in 2–3 doses	

TABLE 45. *Daily Dosage and Routes of Administration of Antimicrobial Agents (Continued)*

SUBCUTANEOUS	INTRATHECAL	AEROSOL	INTRA-PERITONEAL, INTRA-ARTICULAR, INTRAPLEURAL	ADULT OR MAXIMUM DOSE
				Oral—2.0 gm./day IM or IV—1.0 gm./day
				1.5–4.0 million u./day
				Oral—2.0 gm./day IM—800 mg./day IV—3.0 gm./day
				12.0 gm./day
		2 ml. q.i.d. (50,000 u./ml.)	10,000–20,000 u./ml.	20–100 million u./day
				4.0–6.0 gm./day
	<2 yrs., 2 mg./day or every other day >2 yrs., 5 mg./day (0.5–1.0 mg./ml.)		1.0 mg./ml.	Oral—500 mg./day Parenteral—200 mg./day Intrathecal—10 mg./day
				1–2 gm./day
	1.0 mg./kg. or 20 mg./day (5 mg./ml.)	2 ml. q.i.d. (150 mg./ml.)	50 mg./ml.	2.0 gm./day

TABLE 45. *Daily Dosage and Routes of Administration of Antimicrobial Agents (Continued)*

AGENT	ORAL	INTRAMUSCULAR	INTRAVENOUS
Sulfonamides* Sulfadiazine; sulfisoxazole (Gantrisin); Triple Sulfonamides (oral)	120 mg./kg. in 4 doses		120 mg./kg. (50 mg./ml.) in 4 doses
Succinylsulfathiazole (Sulfasuxidine)	200 mg./kg. in 4 doses		
Chlortetracycline (Aureomycin)	20–40 mg./kg. in 4 doses		12 mg./kg. in 2 doses (1 mg./ml.)
Oxytetracycline (Terramycin)	20–40 mg./kg. in 4 doses	12 mg./kg. in 2 doses	12 mg./kg. in 2 doses (1 mg./ml.)
Tetracycline (Achromycin; Panmycin; Sumycin; Tetracyn)	20–40 mg./kg. in 4 doses	12 mg./kg. in 2 doses	12 mg./kg. in 2 doses (1 mg./ml.)
Demethylchlortetracycline (Declomycin)	12 mg./kg. in 4 doses		
Vancomycin (Vancocin)			40 mg./kg. in 2–4 doses or continuous IV (2.5–5.0 mg./ml.)

* First dose should be doubled.

TABLE 45. *Daily Dosage and Routes of Administration of Antimicrobial Agents (Continued)*

SUBCUTANEOUS	INTRATHECAL	AEROSOL	INTRA-PERITONEAL, INTRA-ARTICULAR, INTRAPLEURAL	ADULT OR MAXIMUM DOSE
120 mg./kg. (25 mg./ml.) in 2–4 doses				3–4 gm./day
				8.0 gm./day
			5 mg./ml.	2.0 gm./day
		1 ml. b.i.d. (50 mg./ml. in 75% propylene glycol)	5 mg./ml.	2.0 gm./day
			5 mg./ml.	2.0 gm./day
				600 mg./day
				4.0 gm. first day 2.0 gm./day thereafter

SOME BASES FOR JUDGMENT IN THE USE OF ANTIMICROBIAL AGENTS

B. M. KAGAN, M.D.

In the study of antimicrobial agents one must be prepared for change. Change is a biologic characteristic of both the attacking organism and the human host. One can anticipate, therefore, the need for continuous search for newer antimicrobial agents and continuous re-evaluation of the everchanging relations among microbes, antimicrobial agents, and man.

Literally thousands of antimicrobial agents have been isolated. Most of these never reach a human being because they are too toxic for animals. Some are also found to be too antihuman. A few which are toxic for microbes, yet relatively safe for human beings, continue to be found, although at a slower rate in the past few years.

Of 6 new antibiotics described in 1958, only two have survived—vancomycin and erythromycin propionyl ester (Ilosone). Of eight described in 1959, only four have survived—Coly-Mycin, paromomycin (Humycin), alpha phenoxyethylpenicillin (Syncillin) and demethylchlortetracycline (Declomycin). Two of these are similar to older agents, and the other two were derived from older agents.

Much important information about the existing agents, such as basic pharmacologic data, is still needed, and even more information is needed about infectious disease, such as its natural history and changing etiology. For example, what may be the most common cause of laryngotracheobronchitis in one season and in one locality may not be the same for another season or another locality. As is well known to practicing physicians, knowledge of "what is going around now," its cause and the antimicrobial agent, if any, to which it responds, is an essential that no text can provide today.

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Sometimes knowledge of the pharmacology of these drugs is extremely helpful. For example, in the presence of a staphylococcal enterocolitis or empyema of the gallbladder, erythromycin (Ilotycin, Erythrocin) is particularly useful, since it is excreted in large amounts into the gut through the biliary tree and is excreted in this area in larger amounts than is the propionyl ester (Ilosone) or its derivatives. On the other hand, the propionyl ester of erythromycin (Ilosone) provides higher blood and tissue levels elsewhere in the body.

Another example is infection in the presence of renal failure in a patient. If a tetracycline drug is desired, chlortetracycline is preferred to the other forms because it is destroyed in the tissues rather than being so dependent, like the other tetracyclines, on renal excretion for elimination.

Except in the newborn, the pharmacologic bases for choice among the antimicrobial agents are basically the same for adults as they are for infants and children. The differences in clinical application are principally due to the differences in the causative agents of disease in different age periods. A good example is meningitis. In the premature infant and in the newborn infant, meningitis is most often caused by *Escherichia coli*. For meningitis in this age group, therefore, at least until the bacteriologist reports on the culture, streptomycin, chloramphenicol or tetracycline would be at least one of the drugs of choice. Between the ages of one and three years meningitis is more likely to be due to the influenza bacillus (*Hemophilus influenzae*), and streptomycin or chloramphenicol is the initial drug of choice. On the other hand, in children over three years of age, meningitis is most often caused by the meningococcus—in which case sulfonamide, with or without penicillin, would be important in the initial therapy. Thus knowledge of the most likely causative organism is an essential step in the initial choice of the most effective drug. There is, therefore, a new sequence of clinical thinking when a serious infection must be treated. A strictly clinical diagnosis is not enough. The clinician must make a presumptive etiologic diagnosis based upon probability and begin therapy with the most promising drug or drugs. One cannot at present hope to treat for every possible causative organism. The use of too many drugs may cause more harm than good.

In the newborn, most sepsis is due to either *E. coli* or the staphylococcus; bacterial pneumonia under one year of age is today most often due to the staphylococcus; most osteomyelitis also is due to the staphylococcus (although in sickle cell disease, osteomyelitis is apparently often due to salmonella); an otitis media which has not responded to adequate dosage of penicillin, sulfonamide or tetracycline is likely to be due to the staphylococcus or pseudomonas. A severe throat infection which has not responded to penicillin is not likely to be due to beta

hemolytic streptococcus of the Lancefield group A variety, which might lead to rheumatic fever or acute glomerulonephritis. One must search for another cause and, of course, different therapy. In various situations in which, wisely or not, prophylactic drugs have been used and during which time fever has appeared, it is most likely that the superimposed infection is one which will not respond to the usual doses of the drugs which have already been given. Unfortunately, the superimposed infections are often difficult to treat because they tend to be caused by resistant staphylococci, or such organism as pseudomonas, proteus and monilia.

Today the therapy of choice in infections depends more upon the nature of the microorganism than upon the area of the body affected. It is still important to know the site of the infection, but principally because it gives us a lead as to the most probable causative agent. In addition, the tissue in which the infection resides determines the choice to some extent, depending upon relative concentration of the drug in that tissue.

Once the clinical diagnosis has been made and the site of the infection determined, a tentative working etiologic diagnosis can often be made before the bacteriologist can report on the cultures. Table 46 at the end of this clinic can be helpful at this point.

A culture, ideally taken before any drug is started, may be the second determining step in the decision as to whether the drug or drugs so chosen should be continued. Nevertheless the result of the culture is generally secondary in importance to the clinical response. The clinical response can often have been estimated by the time the reports of the culture are available. If the response is favorable, the therapy may usually be continued even though the report on sensitivity indicates that the drug used was among the least effective or was even without effect "in vitro." In such cases one should be guided by the clinical response rather than the laboratory report except, uncommonly, when it is clear that the immediate favorable clinical response is misleading and possibly unrelated to the prescribed antimicrobial therapy.

In infections which have not yet responded, testing for sensitivity in vitro is another step to further pinpoint the drug of choice. Such tests are especially important in serious infections due to such organisms as proteus, whose species vary greatly in susceptibility to the different agents. If the patient does not respond to initial therapy, the information thus obtained may prove helpful in choosing more effective therapy in protracted or serious infections. The usefulness of a combination of drugs which the patient is receiving may be estimated by testing the antibacterial effect of the patient's serum against the specific infecting organism. For example, in endocarditis, ideally it should be possible to dilute the patient's serum 16 or more times and obtain

a bactericidal effect against the infecting organism. Unless one can obtain this effect with a dilution of at least four times, a favorable clinical response may not result.

The proper dose for the correct length of time is, of course, our goal. Sometimes information about dosage is lacking. For example, note the wide range of dosage for kanamycin in the newborn. the dosage given in Table 44 (p. 1279), though wide, is a compromise from the much wider range recommended by experts in this field. The tetracyclines and erythromycin tend to accumulate if the dose is only a little higher than that recommended. Toxicity of intramuscular polymyxin B is closely related to larger doses. It seems to be minimized, for example, by using smaller, individual doses given at shorter time intervals. When penicillin is given far in excess of that needed for therapeutic effect, freedom from toxicity is remarkable. This may be due perhaps to the fact that penicillin does not readily pass the wall of human cells, whereas it readily enters bacterial cells. This should not lead us to give ever-increasing doses. Eagle's work shows that for some bacteria there is a range of concentration of penicillin for optimum bactericidal activity above and below which it is not as effective.

The best judgment depends upon adequate evaluation of the total situation. This includes a tentative or final etiologic diagnosis, knowledge of the tissue affected, and pharmacology of the drug, giving a large enough amount of the drug to which the etiologic microorganisms are susceptible, by the proper route and as early as possible, and continuation of such treatment for an adequate time to ensure the eradication of the infection.

A single bactericidal agent is generally preferable to a single bacteriostatic one. A well chosen narrow-spectrum antibiotic is more desirable than a less specific broad-spectrum antibiotic.

Antibiotic combinations should be reserved for mixed infections, for delaying the emergence of resistant strains, or for cases in which the evidence is substantial that combined therapy will be better than either agent in the pair. Combinations are also justified in an acute infection when temporary cover is necessary while awaiting bacteriologic diagnosis, or when laboratory investigations fail to isolate a pathogenic organism, and the etiologic agent remains obscure. Selection and wise use of combinations are important, but these should not be used as short cuts or as devices to avoid responsibility for establishing an accurate diagnosis and initiating specifically directed antibiotic therapy.

Use of commercially prepared mixtures should be avoided as much as possible. Inadequate amounts of drugs are often used. Some mixtures include inferior drugs. The fixed ratios are not likely to be appropriate in many situations even if the individual components are. Claim for synergism can be made only for a specific strain of a bacterium, and

none of the available combinations has been proved to be more effective than the best of the individual components. They tend to increase the development of sensitivity by the patient, increase the incidence of side effects, and to confuse the clinical picture and management. Furthermore, their use unfortunately often leads to a sense of false security and the development of resistant infections or superinfections, and tends to delay efforts toward a specific diagnosis.

The antimicrobial agents may fail to give expected favorable results:

1. When they are used in treatment of undiagnosed fever or disease.
2. When they are used in treatment of culture reports rather than patients.
3. When there is poor choice of drug, choice of route or inadequate or improper dosage or intervals between doses, or the use of interfering drugs such as kanamycin and dimethoxyphenylpenicillin (Staphcillin or Dimocillin) or oral tetracycline and aluminum hydroxide.
4. When there is failure to obtain adequate concentration at the site of infection, especially when circulation is poor, as in a well walled-off abscess, chronic leg ulcer, fibrotic lesion or cavity, malignancy or foreign body.
5. When there is delay in starting proper treatment.
6. When insufficient attention is given to host resistance as through control of hematologic status, diabetes, fluid and electrolyte balance, shock, agammaglobulinemia, and so forth.
7. In presence of conditions which do not respond to these agents, such as malignancy.
8. In the presence of a mixed infection.
9. When there is overdependence on culture reports or sensitivity tests.
10. When there is failure to recognize need for surgical drainage or debridement.
11. When there is reliance, even in part, upon these drugs to replace aseptic technique.
12. When there is lack of judgment in considering patient risk from use of the drug versus seriousness of the disease.
13. When the same therapy is continued in an acute infection in spite of failure to respond after three to four days of adequate dosage or in the presence of recurrence of fever, or appearance of illness again after improvement had clearly begun and while the patient continues to receive the same drug.
14. When there is lack of frequent re-evaluation of patients receiving such therapy with attention to the fact that new, persistent or recurrent disease may be easily masked, e.g. mastoiditis, appendicitis or even meningitis.

There are real hazards in the use of the antibiotics, as well as bene-

fits. Although in general they are less common in children than in adults, untoward effects are so frequent that they must always be kept in mind. They can be reduced by not giving the drugs for minor ailments, by avoiding local application of systemically useful ones, by avoiding depot types unless needed, by giving preference to the oral route, and by avoiding simultaneous injection of other possible antigens. The first probably is the most important; i.e. avoid giving them when they are not necessary. Much of the sensitivity to antibiotics is avoidable. Most of the antibiotics used are wasted. Between 20 and 50 tons of penicillin are being sold in this country each year. It is estimated that one out of every 4 people in our country received penicillin in 1955—that 90 per cent was wasted.

In one small community where careful records were kept, the observers accepted almost any reason as valid for the use of antibiotics, even a 1-degree rise in temperature above normal. In spite of this, they found that antibiotic therapy had not been indicated in over 50 per cent of the cases.

The World Health Organization reported that in the United States alone, an estimated 1000 persons died by 1957, after improper use of penicillin. Fortunately, not more than 25 out of every 10 million penicillin injections leads to serious consequences. Of these, however, three may be fatal.

After an injection of penicillin it has been estimated that some reaction may be expected in 2.5 per cent of children, in 5 per cent of nonallergic adults, and 15 per cent of persons with an allergic diathesis. The risk with oral administration is less, estimated at about 0.2 per cent. Reaction rates are said to be increasing by 1 per cent each year, possibly because of prior sensitizing doses of penicillin. Reactions, however, also occur in persons not known to have received penicillin previously.

Some workers feel that the most dangerous kind of penicillin reaction, anaphylaxis, may be anticipated if an immediate whealing reaction occurs on cutaneous or intracutaneous testing. Delayed intracutaneous reactions, i.e. of 28 to 48 hours, may presage a delayed reaction such as serum sickness or urticaria. These tests are not always reliable. They should be done particularly in patients with an allergic background. If parenteral administration is necessary in such patients, the scratch test, using 10 units of penicillin, is perhaps the safest and best test. Especially when allergy is suspected, it is wise to inject the drug into the arm at a low enough level so that a tourniquet may be applied if a severe reaction ensues. Preparation to meet such emergencies is now incumbent upon the physician. These preparations should include availability of a tourniquet, sterile syringes, epinephrine, an antihistamine for parenteral use, and, if possible, oxygen. The epinephrine and antihistamine should be given intravenously. The airway should be kept

open, and oxygen administered. The immediate measures may helpfully be followed by intravenous administration of hydrocortisone or ACTH or intramuscular or oral administration of cortisone.

Our studies have shown that some so-called anaphylactic reactions could be due to accidental intravenous injection of the commonly used aqueous suspension of procaine penicillin. Withdrawal of the syringe plunger to avoid intravenous injection is thus essential.

Drug fever due to antibiotics is probably common, although seldom recognized as such. Persistence of fever and often recurrence of fever during therapy may be due to superinfection occurring as a result of the antibiotic. This calls for re-evaluation of the patient, not merely continuation of the therapy or increasing the dosage.

Novobiocin has produced a high incidence of skin rashes, possibly allergic, especially in children. Likewise probenicid (Benemid) produces more skin rashes in children than it does in adults.

Toxicity due to drugs such as chloramphenicol is now well known, and an important lesson can be learned from our experience with it. The following statement from the Committee on the Fetus and the Newborn of the American Academy of Pediatrics is pertinent:

> It is a basic premise of pediatrics that physical size is not the most important difference between children and adults. There is increasing awareness that it is also necessary to make more than a quantitative distinction between infants and children. The fetus and the newborn infant often behave so differently as to warrant consideration as separate categories of the human species. This necessitates re-evaluation of the effects of drugs independently in each category of the human so that they may be used safely.
>
> Existing drugs and agents which are developed in the future for use in the fetus and in infants must be subjected to more extensive preclinical investigation than is being carried out at the present time. The pharmacologic responses of the immature human may differ greatly both quantitatively and qualitatively from those of the adult. As a result, data obtained from tests in mature animals and human adults or older children cannot be accepted as a satisfactory basis for recommendations concerning the fetus and infant.
>
> The pharmacologic properties of drugs should be studied *in vitro* and *in vivo* in the fetus and newborn animal and compared with those in the adult of the same animal species. Of particular importance would be knowledge of the LD_{50} dose response, metabolism, and distribution of the drug. These determinations should be performed in two or more animal species (a rodent and non-rodent species). Pharmacodynamic actions and clinical effects of drugs in humans should be assessed in clinical situations in which they may be useful.
>
> In order to pursue these principles, it is recommended that drug labels should specifically indicate the extent of existing information concerning the use of the agent in the fetus and the infant. When there have been no pharmacologic studies of a drug in immature subjects an explicit statement of this fact should be indicated on the drug label or in a readily available package leaflet. Physicians who administer drugs to the fetus and the infant must be alert to unusual effects in this subdivision of the human species.

Severe neuritis has been described in infants and adults in which sensory losses or disabling motor paralyses followed intramuscular injection of penicillin, streptomycin or tetracycline. The disabilities per-

sisted for months in some cases and in a few seemed permanent. The sciatic nerve was involved most frequently after intragluteal injections, though the deltoid region was affected in some. The immediate onset of symptoms in some cases suggested a more or less mechanical injury. In others, notably after injection of penicillin, the symptoms appeared only after several days, leading one to believe that the effect was related to the known toxicity of penicillin for nerve tissue. The complication is admittedly of infrequent occurrence, but the consequences are disastrous. Because of this, some have suggested injection in the anterior outer aspects of the thigh.

Prophylaxis may be justified when one is dealing with specific infections such as those caused by hemolytic streptococci or those due to meningococci, gonococci and a few others. There is little justification for antibiotic prophylaxis against the bacterial world at large.

In one study 130 patients with measles received antibiotics prophylactically. About 30 per cent had superimposed bacterial infections. This occurred in only about 15 per cent of 298 such cases not receiving antibiotics. Complicating infections developed in only 16 per cent of 165 cases of bulbar poliomyelitis not receiving drugs, but in 53 per cent of 63 similar cases given so-called prophylactic antibiotics. Such "prophylaxis" does little more than ensure that the superimposed infections will be resistant to the antibiotics used.

One survey in 1956 showed that two thirds of all patients admitted, exclusive of the obstetric and newborn services, received antibiotics. Most was given "prophylactically"' before operation.

In another study bacterial complications in clean operations were five times as high in "prophylactically" treated patients as in patients who are not given antibiotics "prophylactically."

There are few situations in which prophylactic antibiotics are effective. Some legitimate indications for prophylaxis are as follows: penicillin against group A beta hemolytic streptococci; sulfadiazine against meningococcus; penicillin against pneumococcus and streptococcus, particularly in the presence of agammaglobulinemia; prevention of endocarditis in susceptible patients having dental work; penicillin against gonococcus and before surgical treatment for infected areas such as tuberculous lung; sulfonamides or other agents for shigella dysentery in a closed population.

Although used commonly in the following situations, the value of such prophylaxis is doubtful: women with prolonged and difficult labor; surgery involving division of a bronchus; bowel sterilization before bowel surgery; and contaminated wounds of violence.

In the following situations in which "prophylaxis" is often used, it is not only valueless but sometimes dangerous: virus infections; routine preoperative or postoperative care; comatose patients; patients with

urinary bladder retention catheters; bulbar poliomyelitis; tracheotomized patients; very ill patients with noninfectious diseases; patients receiving steroids (except to prevent a specific disease in a high-risk group, or antituberculous therapy patients, or patients with sarcoidosis).

Finally, the remarkable effectiveneess of antimicrobial therapy should not blind the physician to the importance of host resistance. Even with bactericidal agents, host resistance can be the decisive factor. One should, therefore, keep in mind that before this era, lives were saved from serious infectious disease by the judicious use of whole blood, plasma or serum, gamma globulin, and attention to such essentials as nutritional status, fluid and electrolyte balance, and control of diabetes These other measures should always be considered either instead of or in conjunction with the use of antimicrobial drugs.

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TABLE 46. *Tentative Choice of Antimicrobial Agent in Common Infections**

INFECTION	MILD TO MODERATE SEVERITY, SOFT TISSUE OR LOCALIZED	SERIOUS—BLOOD, HEART, BRAIN, BONE, LUNG	ENTERIC (ORAL TREATMENT)
Aerobacter aerogenes†	Tetracycline Streptomycin Chloramphenicol	Kanamycin Neomycin Tetracycline Streptomycin Chloramphenicol Polymyxin	
Actinomyces	Penicillin Sulfonamide Tetracycline Chloramphenicol	Penicillin Sulfonamide Tetracycline Chloramphenicol	
Alcaligenes faecalis†	Tetracycline Chloramphenicol Streptomycin Kanamycin	Streptomycin Tetracycline Chloramphenicol Kanamycin	
Brucella	Tetracycline+ Streptomycin Chloramphenicol	Kanamycin Tetracycline+ Streptomycin and/or chloramphenicol	
Clostridium perfringens (welchii)	Penicillin Erythromycin Tetracycline Kanamycin	Penicillin Erythromycin Kanamycin	Penicillin Kanamycin Erythromycin
Clostridium tetani	(Antitoxin) Penicillin	(Antitoxin) Penicillin	

Constant change is a characteristic of biologic relations. Many biologic factors may cause changes in relative merit of different drugs at different times.

TABLE 46. *Tentative Choice of Antimicrobial Agent in Common Infections* (Cont.)*

INFECTION	MILD TO MODERATE SEVERITY, SOFT TISSUE OR LOCALIZED	SERIOUS—BLOOD, HEART, BRAIN, BONE, LUNG	ENTERIC (ORAL TREATMENT)
Diphtheria (C. diphtheriae)	(Antitoxin) Erythromycin Penicillin Tetracycline Chloramphenicol	(Antitoxin) Erythromycin Penicillin Tetracycline Chloramphenicol	
E. coli	Tetracycline Sulfonamide Streptomycin Chloramphenicol Furadantin (renal)	Streptomycin Chloramphenicol Kanamycin Neomycin Polymyxin B Coly-Mycin	Neomycin Kanamycin Chloramphenicol Polymyxin B Coly-Mycin
Gonococcus (N.gonorrhoeae)	Penicillin Tetracycline Chloramphenicol Erythromycin	Penicillin Tetracycline Chloramphenicol Erythromycin	
H. influenzae	Penicillin+ streptomycin Tetracycline Sulfonamide Chloramphenicol	Chloramphenicol+ streptomycin Penicillin+ streptomycin (croup)	
Klebsiella pneumoniae† (Friedländer's bacillus)	Streptomycin+ sulfonamide, penicillin or chloramphenicol Kanamycin Polymyxin B	Streptomycin+ sulfonamide penicillin chloramphenicol Kanamycin Polymyxin B Neomycin Tetracycline Chloramphenicol	
Meningococcus (N. meningitidis)	Sulfonamide Penicillin Chloramphenicol	Sulfonamide Penicillin Chloramphenicol	
Moniliasis (C. albicans)	Amphotericin B Nystatin	Amphotericin B Nystatin	Nystatin Amphotericin B
Pneumococcus	Penicillin Erythromycin Tetracycline Chloramphenicol Sulfonamide	Penicillin Erythromycin Tetracycline Chloramphenicol Sulfonamide	
Pertussis (B. pertussis)	Tetracycline Sulfonamide Chloramphenicol	Tetracycline Chloramphenicol Sulfonamide	

TABLE 46. *Tentative Choice of Antimicrobial Agent in Common Infections* (Cont.)*

INFECTION	MILD TO MODERATE SEVERITY, SOFT TISSUE OR LOCALIZED	SERIOUS—BLOOD, HEART, BRAIN, BONE, LUNG	ENTERIC (ORAL TREATMENT)
Proteus (indole-positive)† **Proteus morganii** **Proteus rettgeri** **Proteus vulgaris**	Furadantin (renal) Novobiocin Penicillin (large doses) Kanamycin Sulfonamide Chloramphenicol Tetracycline	Kanamycin Streptomycin Novobiocin Penicillin (large doses) Chloramphenicol Tetracycline	Sulfonamide Kanamycin Neomycin Novobiocin
Proteus (indole-negative) **Proteus mirabilis**	Penicillin Tetracycline Chloramphenicol Streptomycin	Penicillin Tetracycline Chloramphenicol Streptomycin	
Pseudomonas aeruginosa (B. pyocyaneus)	Polymyxin B Coly-Mycin Furadantin (renal) Kanamycin	Polymyxin B Coly-Mycin Kanamycin Neomycin	Polymyxin B Neomycin Kanamycin
Salmonella (not typhosa)	Tetracycline Chloramphenicol Kanamycin	Chloramphenicol Tetracycline Kanamycin	Tetracycline Chloramphenicol Kanamycin Furazolidone
Salmonella typhosa	Chloramphenicol Tetracycline Kanamycin Sulfonamide	Chloramphenicol Tetracycline Kanamycin Sulfonamide	Chloramphenicol Tetracycline Kanamycin Sulfonamide
Shigella	Sulfonamide Tetracycline Chloramphenicol	Sulfonamide Tetracycline Chloramphenicol	Sulfonamide Tetracycline Chloramphenicol Polymyxin B Furazolidone
Staphylococcus aureus (M. pyogenes)	Erythromycin Penicillin (if sensitive) Staphcillin (if penicillin-resistant) Novobiocin Chloramphenicol Triacetyloleandomycin Neomycin (skin)	Penicillin ± bacitracin Staphcillin (if penicillin-resistant) Kanamycin Vancomycin Ristocetin Erythromycin+ others Novobiocin+ others Neomycin	Erythromycin Neomycin Kanamycin
Streptococcus, beta hemolytic (pyogenes)	Penicillin Triacetyloleandomycin Erythromycin	Penicillin	

TABLE 46. *Tentative Choice of Antimicrobial Agent in Common Infections* (Cont.)*

INFECTION	MILD TO MODERATE SEVERITY, SOFT TISSUE OR LOCALIZED	SERIOUS—BLOOD, HEART, BRAIN, BONE, LUNG	ENTERIC (ORAL TREATMENT)
Streptococcus faecalis,† Str. viridans†		Penicillin+ streptomycin Penicillin+ erythromycin Penicillin+ bacitracin Kanamycin Vancomycin Ristocetin	Kanamycin Neomycin
Syphilis (T. pallidum, spirochaeta pallida)	Penicillin Tetracycline Chloramphenicol Erythromycin	Penicillin Tetracycline Chloramphenicol	
Tuberculosis (M. tuberculosis)	Isoniazid Streptomycin Para-aminosalicylic acid (PAS)	Streptomycin Isoniazid ± PAS	

* Pending bacteriologic identification and results of sensitivity testing.

† Rely more heavily on sensitivity in vitro. Effects of drugs are variable and often poor.

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